This article describes how configuration software changes are commonly tracked and managed today using "paper-based" configuration audit trails, the shortcomings of the paper-based solutions, and a new automated computer-based configuration audit trail that addresses the shortcomings of the traditional paper-based solutions.

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Addressing 21 CFR Part 11 Requirements with an Automated Configuration Audit Trail and Version Management System

by David Deitz

Introduction

Designing and implementing process control software is an interactive and ongoing process. There are several reasons for this. In some instances, specifications for the process control software lack the necessary detail to accurately design and implement the required control in a single attempt. In others, the process equipment that the process control software must interact with lacks features or functionality that it was assumed to support at the time the process control software was designed. Even in a 'perfect' situation in which the process control software was implemented exactly as specified and no process equipment issues needed to be addressed, configuration software changes would undoubtedly be required as the process is optimized to maximize product quality and throughput.

When process control software is designed and implemented within a facility that is regulated by the FDA, procedures must be put in place to ensure that the software can be validated to perform as expected. In this case, the need for change control policies and procedures has been documented in numerous guidelines and papers on computer systems validation. In addition, the computer systems validation lifecycle models developed by the PDA and GAMP both identify the importance of ongoing change monitoring and change management.

A Conventional Approach: The Paper-Based Configuration Audit Trail

With the understanding that configuration software changes will occur, and that change control is an integral component of computer systems validation, all manufacturers who operate regulated facilities have implemented some form of a configuration software change management system. Presently, the overwhelming majority of these facilities have implemented paper-based systems for tracking configuration software changes (i.e. a paper-based configuration audit trail).

As an element of the overall validation protocol, a SOP is usually developed to guide individuals who may modify the process control software (e.g. automation and control engineers, process engineers, instrument technicians, etc.) as to how software changes are to be docu-

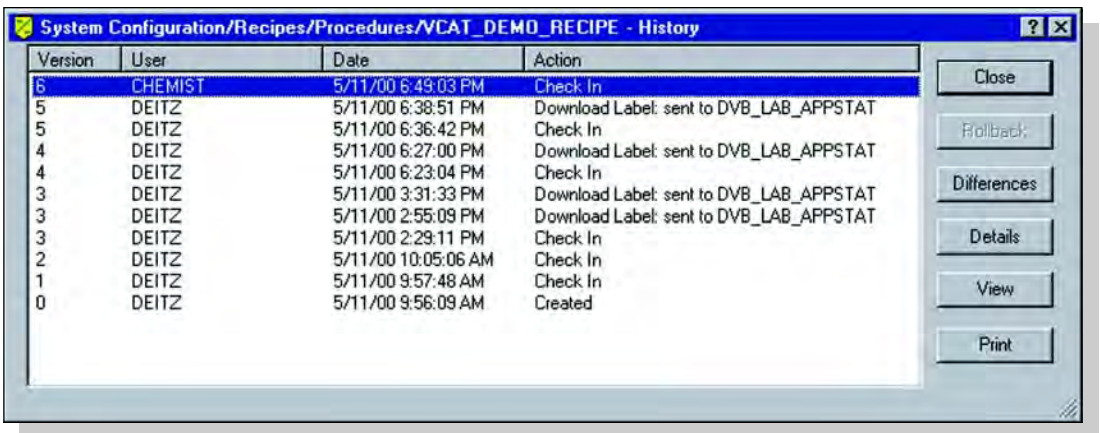

Figure 1. Software module version history.

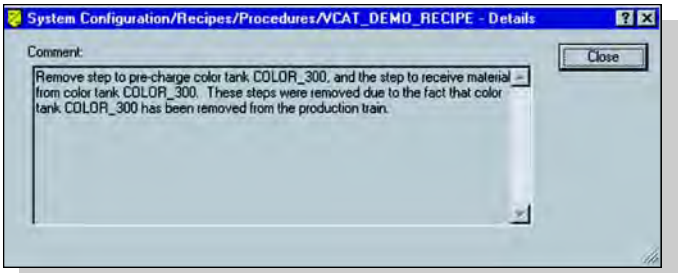

Figure 2. Item "check-in" comment.

mented. For the remainder of this article, individuals who may modify the process control software will be generically referred to as "configuration software engineers." By carefully following and adhering to the requirements defined in the SOP, the configuration software engineers are manually generating a configuration audit trail. Usual requirements spelled out in a software change management SOP that are specific to documenting configuration software changes often include the following:

- Every software file must contain a file header that supports user-entered comments.
- The configuration software engineer is responsible for updating the file header with a remark that documents the scope of the change whenever the software is modified.
- The configuration software engineer is responsible for including remarks within the software as necessary to easily and readily identify portions of the software that have been modified.
- Remarks placed in the file header should include the name of the individual who implemented the change, as well as the date and time that the change was made.
- The file's version identifier should be updated after any alteration is made to the configuration software.
- A paper printout of the modified software must be generated.
- The paper printout of the changed software must be filed and available for future inspection and review.

It is apparent from this list of tasks that the manual effort required to develop and produce a configuration audit trail is substantial and places a significant burden on the configuration software engineers.

Drawbacks of the Paper-Based Configuration Audit Trail Approach

Although paper-based software audit trails have been used extensively by industry for many years and are still the custom today, the approach is not ideal. There are several potential drawbacks to the paper-based audit trail:

- **Training and familiarization with the SOP.** The paper-based system relies on each configuration software engineer to have a thorough understanding of requirements in the change management SOP that are pertinent to the procedures to be followed to adequately document configuration software changes. As such, it is crucial that each member of the project team receives training on the SOP. Providing this training at the beginning of a new project for a new project team can usually be accomplished in an efficient and cost-effective manner. However, as the project progresses through its lifecycle, the project team will continue to evolve. Ensuring that new members of the "evolving" team are sufficiently trained on the SOP is much more challenging, much less efficient, and significantly less cost effective.
- **Consistency and accuracy of the paper-based audit trail.** Because the audit trail is created manually by the configuration software engineers, each engineer is free to decide what level of detail is required to adequately document the changes that they have implemented. This is especially problematic when the configuration software engineer who made the modification and is documenting it is very familiar with the software being modified. In this scenario, configuration software engineers tend to provide a minimal amount of information and detail in their remarks. This can create substantial problems for individuals who are responsible for the software from a long-term perspective (i.e. plant operations personnel). These individuals are very likely to be much less familiar with the software than the configuration software engineer who implemented the modification, and may not be able to readily discern the complete scope of the change based on the limited comment provided.
- **Accountability issues associated with the paper-based audit trail.** With a paper-based configuration audit trail, there is no mechanism to ensure that descriptions of changes are actually recorded at the time the software is being altered, or that the configuration software engineer who made the changes is the individual who actually updated files with the information about the change. Additionally, in the heat of start-up, it is very easy for modifications to be overlooked, and hence go undocumented.
- **Difficulty with definitively linking a version of software that is actually running in the control system to a specific version of the software in a paper-based system.** This paper-based configuration audit trail system does not capture events such as the downloading of a new version of a software module. As such, there is no way to easily assure that the version of a piece of software executing in the controller is identical to a particular version of software in the paper based files.
- **Paper-based audit trail is a document management nightmare.** Significant investments in personnel and space are required to ensure that all the paper versions of the software which are created over the life of the process control system are filed in such a way that they can be readily found for inspection and review.
- **Paper-based configuration audit trail requires the configuration software engineers to spend a significant portion of their time and energy on documenting change rather than optimizing the process.** The use of highly skilled and highly compensated engineers to develop configuration audit trail documentation is an ineffective use of configuration software engineering resources,

and a tremendous cost burden to the project. In addition, the time that configuration software engineers spend on creating paper based documentation is time that can not be spent on improving the operation of the facility to increase production.

- **Paper-based configuration audit trails may not be acceptable to the regulatory agency (i.e. the FDA)**. Process control software is included in the definition of electronic records as defined in 21 CFR Part 11 §11.3(b)(6). Within 21 CFR Part 11, subpart b, §11.10 lists several specific controls and practices that may be required to ensure the authenticity and integrity of electronic records. Controls and practices identified in the section which might be especially relevant to this discussion include items §11.10(e) which states "***Use of secure, computer-generated, time-stamped audit trail to independently record the date and time of operator entries and actions that create, modify, or delete electronic records…,"*** and item §11.10(k)(2) which states ***"Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation."*** Given the statements of §11.10 (e) and §11.10 (k)(2), it is reasonable to conclude that computer based audit trails may be the only acceptable way of tracking changes in electronic records in the near future.

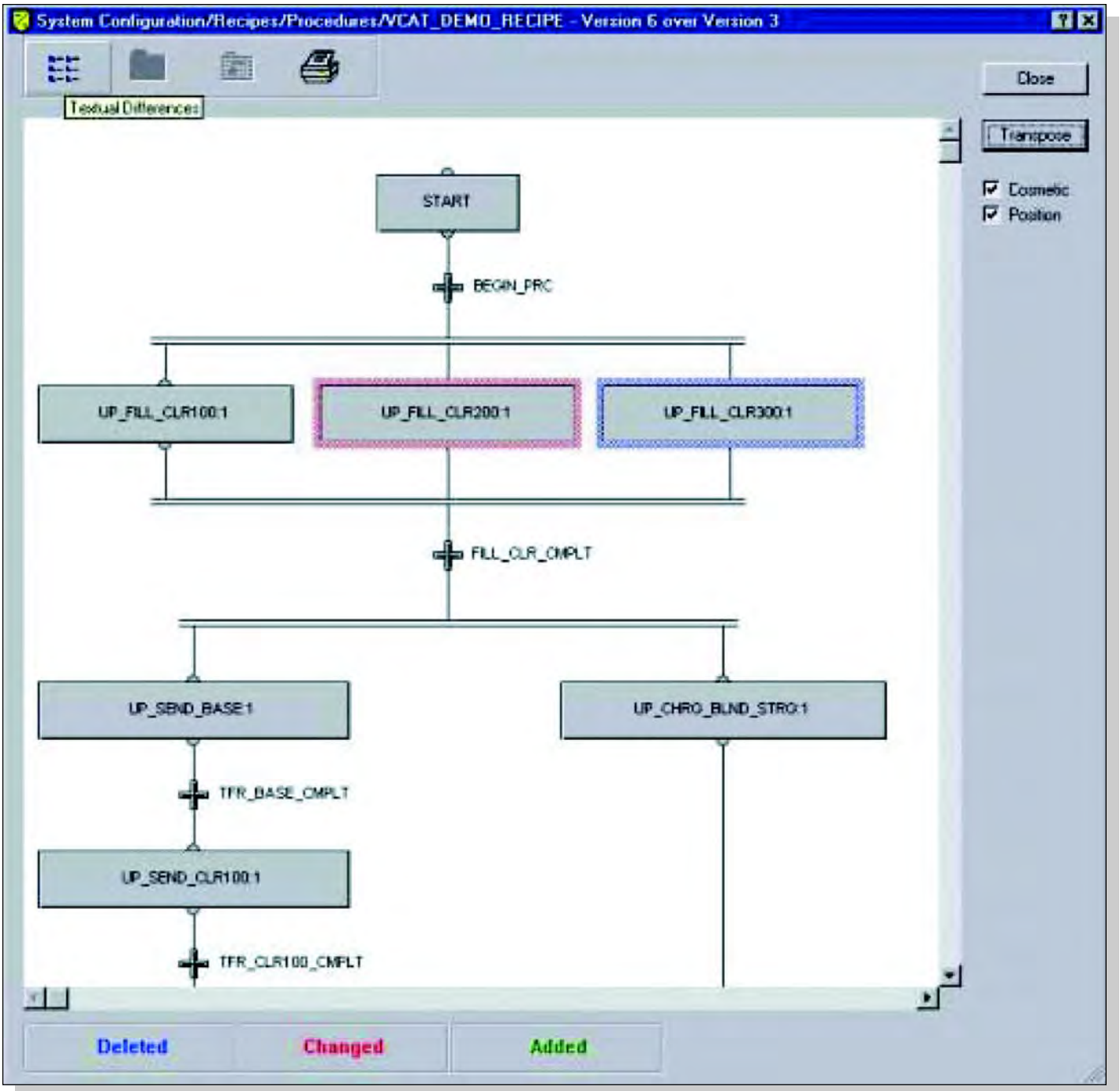

Figure 3. Graphical version-to-version comparison.

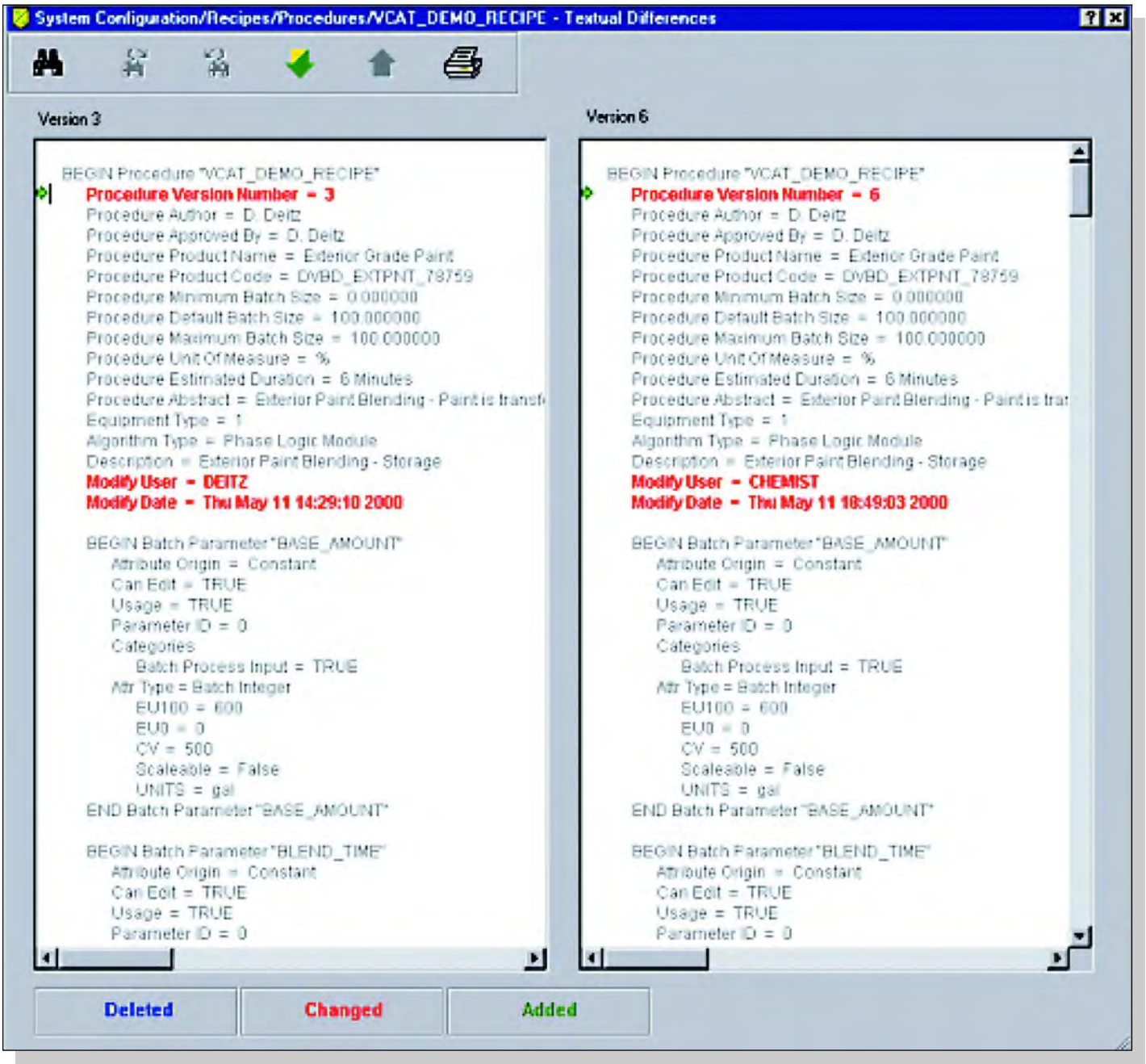

Figure 4. Textual version-to-version comparison: modified data.

While paper-based configuration audit trails have been the custom for the past several years, it is apparent from the list of potential shortcomings associated with this approach that there is room for significant improvement.

A New Method: An Automated Computer-Based Configuration Audit Trail and Version Management System

After reviewing the drawbacks of the paper-based configuration audit trail, one would quickly conclude that significant improvements could be made in the area of software change management if the paper-based configuration audit trail could be replaced by a computer-based system that automatically tracked process control software changes.

One system that contains an automated computer-based configuration audit trail and version management application is the DeltaV system by Fisher-Rosemount Systems. The configuration audit trail and version management software is tightly integrated with the software engineering environment and provides transparent software change tracking, including the automated capture of "who," "when," and "what" type data. Version-to-version comparisons of any software module may be viewed using either a graphical or textual differences viewing feature. The system also provides a mechanism to "roll-back" to an earlier version of a software module, as well as traceability of configuration software versions to the run-time environment. Access to the audit trail and version management system is integrated with and managed by the security system.

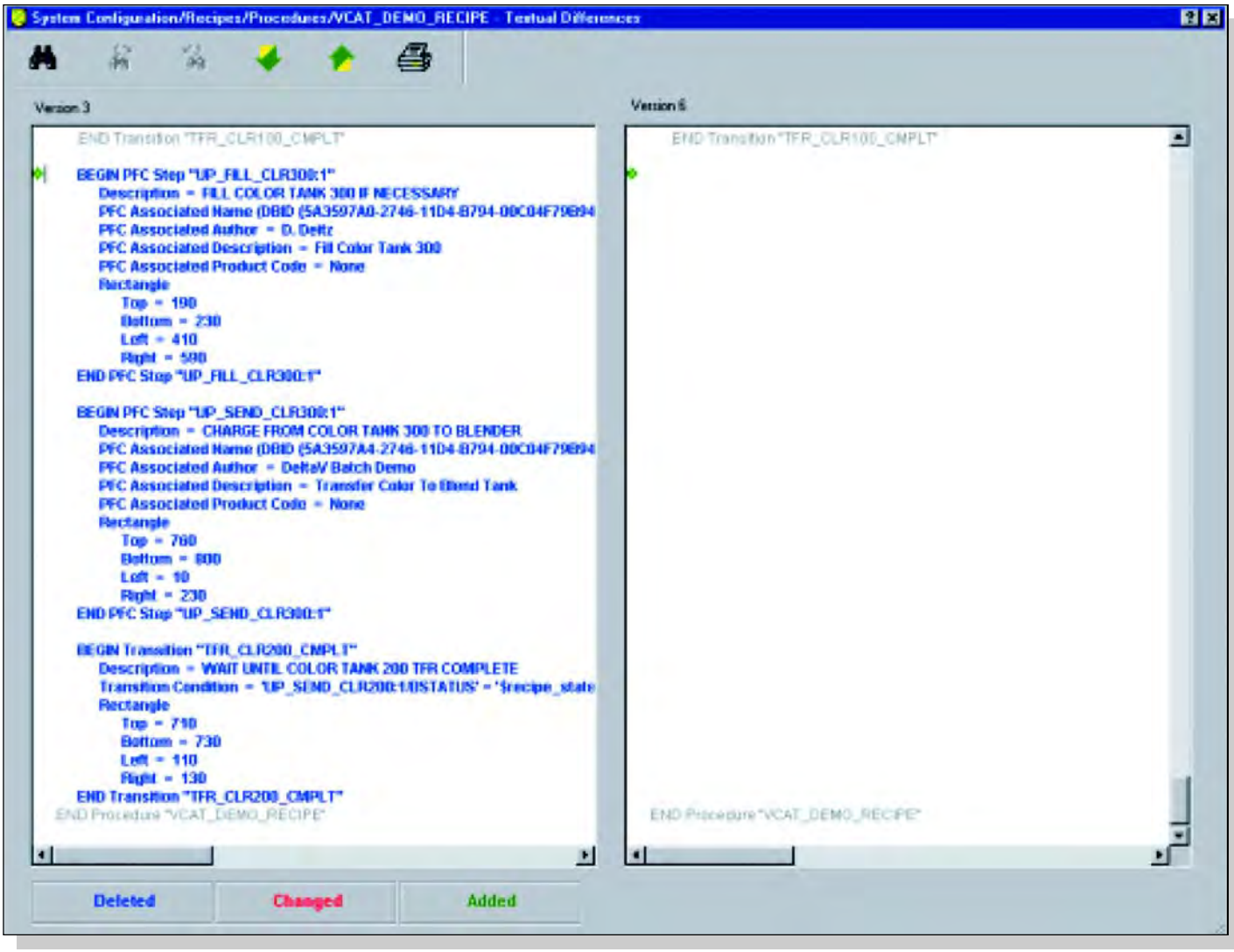

Figure 5. Textual version-to-version comparison: deleted data.

The tight integration between the configuration audit trail and version management system and the software engineering environment facilitates transparent collection of configuration audit trail data, and addresses applicable requirements from 21 CFR Part 11. The following sections of this article discuss the requirement for specific procedures and controls that are enumerated in 21 CFR Part 11, and how these procedures and controls have been implemented in the configuration audit trail and version management application.

The Automated Configuration Audit Trail and Version Management System - Software Revision History and Version-to-Version Comparisons

21 CFR Part 11 specifies that processes and controls shall be employed to ensure the authenticity and integrity of electronic records. Specific procedures and controls relevant to the software revision histories and version-to-version comparison aspects of the automated configuration audit trail and version management system include:

- §11.10(a) "Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records."
- §11.10(b) "The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the Agency…"
- §11.10(e) "Use of secure, computer generated time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records…"

When the configuration audit trail and version management system is enabled, software modules must be "checked-out" by the configuration software engineer before they can be altered. After the altering of an item has been completed, it must be "checked-in" to the configuration audit trail and version management system before it may be downloaded to a control device. When the request is made to check-in a software module, the configuration audit trail application automatically records the name of the user performing the "check-in" and the date and time the "check-in" of the software module was performed. The version identifier for the software module being "checked-in" is automatically updated as part of the "check-in" process. To illustrate this feature, an example of a software module's version history is presented in Figure 1.

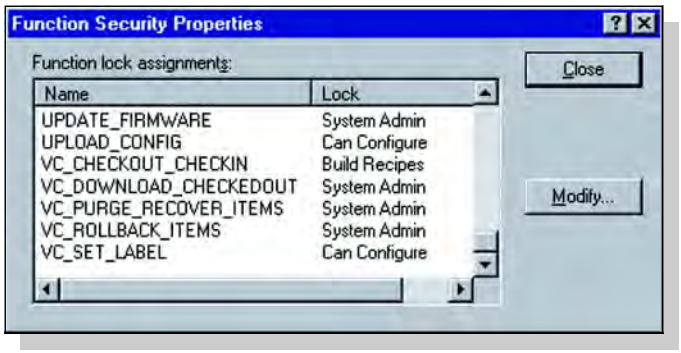

Figure 6. Function security lock assignments.

When a software module is "checked in," the configuration software engineer is offered an opportunity to enter a comment that will be attached to the "check-in" event. The comment field may be used to provide additional detail about the extent of the alteration that was made, enter a revision control number that the change is related to, or provide other detailed information that the configuration software engineer may deem important.

The comment associated with the check-in of an item may be viewed by merely selecting a specific version of the software module from the module revision history (Figure 1), and then selecting the "Details" button on the version history dialog. Figure 2 presents an example of a software module "check-in" comment.

The automated configuration audit trail and version management system collects all of the required version history information automatically as an integral piece of the configuration software development process. For this reason, no special effort is required on the part of the configuration software engineer to collect or manage software module version history data.

Collecting and displaying revision history information is only one part of monitoring and tracking configuration software changes. A second and equally important part of the automated configuration audit trail application is its ability to automatically detect and display changes that have occurred between different versions of a software module.

Since most configuration software modules are developed using graphical configuration techniques, the automated configuration audit trail and version management system has been designed to support graphical version-to-version comparisons. When viewing graphical differences, color-coding is employed to identify information on the diagram that has been added, modified, or deleted. A graphical version-to-version comparison is shown in Figure 3.

Many configuration software changes are alterations to information within a graphical element rather than the actual addition or deletion of a graphical element. When graphical elements contain information that has been altered, they are identified as "changed" elements on the graphical comparison view. However, in many cases, additional details about the change that has occurred within the graphical element are required. To support more detailed analysis, the configuration audit trail and version management system also offers the ability to view "textual" based differences.

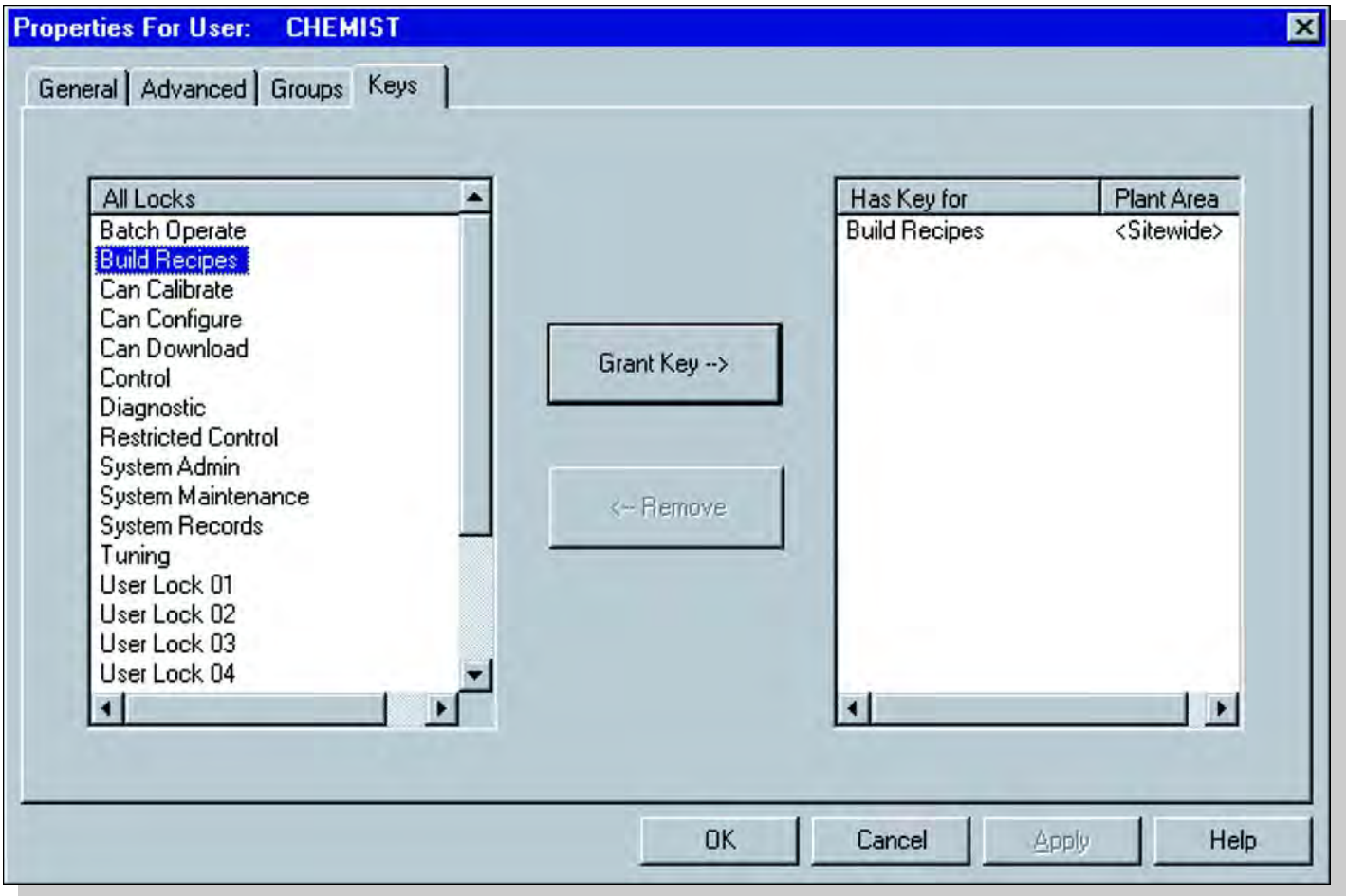

Figure 7. Granting a function lock key to a user.

Textual based differences give a more detailed comparison of information associated with a software module that is not readily viewable in the graphical comparison view (e.g. actions that are defined within a step). In addition, the textual based differences view also gives a mechanism for comparing software modules that do not have graphical views (e.g. a name set). Figures 4 and 5 show the results of a textual version-to-version comparison.

As Figures 4 and 5 clearly depict, the automated configuration audit trail and version management system provides the user with a clear, consistent, and accurate depiction of configuration software engineering changes. Again, as was the case with the software module version history, all the information required to support version-to-version comparisons is collected automatically as an integral part of the configuration software development process, and requires no extra effort on the part of the configuration software engineer.

All revision history information, as well as graphical and textual version-to-version comparisons can be printed for inspection and review, thus ensuring compliance with the procedures and control outlined in §11.10(b).

The Automated Configuration Audit Trail and Version Management System - Version Rollback

21 CFR Part 11 specifies that procedures and controls shall be used to ensure the authenticity and integrity of electronic records. Specific procedures and controls pertaining to the version rollback aspects of the automated configuration audit trail and version management system include:

- §11.10(c) "Protection of records to enable their accurate and ready retrieval throughout the records retention period."
- §11.10(e) "…Record changes shall not obscure previously recorded information…"

There are instances when it is necessary to be able to revert back to a previous version of a software module. For example, in a flexible manufacturing facility, the user may employ different versions of a software module to make different products (e.g. version 3 of a temperature control module is used to make product A, while version 5 of the temperature control module is used to make product B). To serve the requirement to be able to revert back to previous versions of a software module, a "rollback" function has been included in the automated configuration audit trail and version management system.

From the module history dialog, the configuration software engineer can select a previous version of a software module and "rollback" the module to that version. The internal software mechanisms that are used to perform the rollback have been designed to ensure that the rollback to the previous version of software does not obscure any later versions, or preclude the future recall of the later versions.

The Automated Configuration Audit Trail and Version Management System - Configuration and Runtime Software Version Linkages

21 CFR Part 11 contains no specific requirements relating to the ability to correlate version information for a software module in the process control system configuration database and a copy of that module in the process control device. However, by providing mechanisms to ensure that the software modules running in the controller can be linked to a specific version of the software module in the configuration database, the total integrity of the system is enhanced.

The automated configuration audit trail and version management system provides three mechanisms that were specifically implemented to ensure that it is possible to establish a link between a specific version of a software module (as viewed in the software module's revision history) to the version of the software module that is operating in the control device. These three mechanisms include:

- No software module can be downloaded if it is "checked-out" of the configuration audit trail and version management system. This ensures that only versions of the module that are visible in the software module's revision history can be downloaded.
- The downloading of a software module to a control device automatically produces an entry in that module's revision history. The entry in the version history reveals the device that the module was downloaded to. An example of this functionality is depicted in Figure 1.
- The software module version number is downloaded to the control device for all control modules and recipe elements.

By adding this functionality in the automated configuration audit trail and version management system, inspectors and auditors can be assured that the software executing in the control device is, in fact, the same software that exists in the configuration database.

The Automated Configuration Audit Trail and Version Management System - User Access Controls

21 CFR Part 11 specifies that processes and controls shall be employed to ensure the authenticity and integrity of electronic records. Specific processes and controls that are relevant to the user access controls aspects of the automated configuration audit trail and version management system include:

- §11.10(d) "Limiting access to authorized individuals."
- §11.10(g) "Use of authority checks to ensure that only authorized individuals can use the system…"

The configuration audit trail and version management system application is tightly integrated with the system security services. As an example, the system administrator must grant function lock "keys" to individuals in order for those individuals to be able to perform actions such as checking items in and out of the configuration system, performing a version rollback, or setting database labels.

Using these function lock key assignment capabilities, the system administrator has the ability to create a class of users with "read-only" capabilities. By supporting the concept of a "read-only" user within the configuration audit trail and version management application, individuals who need to review and inspect the system configuration can readily do so. However, because these users have a "read-only" authorization, they are prevented by the security system from being able to make any modifications to the configuration software.

Figure 6 presents user locks associated with the configuration audit trail and version management system. Figure 7 displays the dialog that the system administrator interacts with to grant function lock keys to individual users.

The tight integration between the configuration audit trail and version management application ensures that only users who have the required security keys are allowed to access and/or modify the software modules.

Conclusion

At this time, paper-based configuration audit trail and version management systems are still the standard. However, automated computer-based configuration audit trail and version management systems have several advantages over paper-based systems, and as such, are better suited to addressing the requirements of 21 CFR Part 11 which are applicable to the management and tracking of changes to process control software. Computer-based systems are more accurate and reliable than traditional paper-based systems with respect to detecting and documenting configuration software change and also provide functionality that does not exist in a paper-based system.

There are also substantial cost savings to be realized with the use of the automated configuration software and version management application. The tight integration between the automated configuration audit trail and version management application and the process control software development environment significantly reduces the cost of configuration change tracking, and eliminates the requirement for configuration software engineering resources to perform "no-value" work that is better handled by the automated system. By making better use of engineering resources already within the organization, it is frequently possible to execute additional process optimization projects that may significantly improve the corporate bottom line.

In view of the many benefits that an automated configuration audit trail and version management system provides, it is almost a certainty that this approach will quickly become the new standard.

References

1. "Food and Drugs," 21 CFR, Part 11 (Federal Register, U.S. Government Printing Office, Washington, DC, 4/1/99 Edition).

About the Author

Dave Deitz is the DeltaV Batch Product Manager. In this role, he has responsibility for defining the functional requirements for the DeltaV Batch Product Suite, and delivering that functionality to the marketplace.He joined the Fisher Controls systems engineering group in June, 1981, and has held a number of positions of increasing responsibility with Fisher-Rosemount. He has focused almost exclusively on the design and implementation of batch process control systems throughout his career. In 1991, he accepted a position as the pharmaceutical industry consultant for Fisher-Rosemount Systems, and in 1995 was named the DeltaV Batch product manager. Deitz has a BS in chemical engineering from the University of North Dakota and an MS in biochemical Engineering from the University of Texas at Austin. He is a member of ISA, ISPE, and The World Batch Forum.

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Commissioning and Qualification: The ISPE Baseline® Guide

by Christopher Wood

The delivery of manufacturing facilities regulated by FDA or other regulatory authorities pose significant challenges to manufacturers, engineering professionals and equipment suppliers. These facilities are required to meet cGMP regulations while remaining in compliance with all other governing codes, laws and regulations.

The cost and time required to bring such facilities on line has been increasing, in many cases due to inconsistent interpretation of regulatory requirements. The International Society for Pharmaceutical Engineering (ISPE) and engineering representatives from a broad base of healthcare companies have entered into a partnership with the Food and Drug Administration (FDA) to enhance understanding of "baseline" cGMP requirements for facilities.

As part of this initiative, an integrated European and US team of senior pharmaceutical engineering and QA representatives has been working and consulting with the industry to draft the *ISPE Baseline® Commissioning and Qualification Guide*, publication of which is anticipated early in 2001. This guide aims to define key terms and offer a consistent interpretation, while still allowing a flexible and innovative approach to facility design, construction, commissioning and qualification.

This article aims to describe the goals, philosophy and key concepts being suggested within the guide.

Scope

The Guide will address the process of designing, constructing, commissioning and qualifying the facilities, utilities and equipment regulated by FDA or other health authorities. The guide will neither be a standard or a GMP and is not intended to replace governing laws, codes, etc. that apply to facilities of this type.

Neither will strict adherence to the guide guarantee that a facility will be acceptable to FDA or any other regulatory body. While this might be a disappointment to those who seek a "check-box" solution to their qualification problems, the guide does not aim to absolve pharmaceutical manufacturers of the responsibility to think carefully, but to provide a framework within which sensible decisions can be made and supported.

Last, the Guide does not address *Process Validation.* This subject is well defined by FDA and other authorities and substantial guidance already exists.

However *Commissioning* and *Qualification* activities are the foundation upon which *Process Validation* is built. Furthermore, these activities play a crucial role in delivering operationally effective, safe and efficient facilities, utilities and equipment. Therefore, it is important to ensure that a comprehensive approach is undertaken during the commissioning and qualification process. A well conceived and executed commissioning and qualification plan can greatly facilitate a timely and cost effective process validation effort.

Goals

There are two primary goals of the Commissioning and Qualification Baseline® Guide. The first is to bring a common terminology and methodology to the commissioning and qualification process that can be used by manufacturers, facility designers, contractors and equipment suppliers. The second is to provide a system impact assessment process to bring structure and consistency in determining the potential impact of engineering systems on product quality. An important secondary goal is to foster an interdisciplinary team approach to commissioning and qualification.

Philosophy

The basic philosophy promoted by the Guide is that:

- *Good Engineering Practice* (GEP) makes a significant contribution to meeting the regulatory demands of the pharmaceutical industry.

- Where engineering systems may have a *Direct Impact* on product quality, supplementary *Qualification Practices* (in addition to GEP and Commissioning) are required to fully address pharmaceutical industry demands.

- The *Baseline*® approach is to restrict the application of Qualification Practices to Direct Impact Systems and build on the contribution of GEP and Commissioning.

- Good Engineering Practice is a satisfactory approach for Indirect or No Impact Systems.

System Impact

It is the function of the facility, equipment or utility that determines what level of commissioning and qualification are needed:

- **Direct Impact Systems** are expected to have an impact on product quality

- **Indirect Impact Systems** are not expected to have an impact on product quality

This differentiation between system type is important and should determine the attention and effort given to each and by whom. Therefore, the determination as to whether the system is direct or indirect impact is a key issue. **System impact assessment** provides the thought process as well as some key questions that must be addressed in making the assessment.

Some concern has been expressed that designating a system "indirect impact" might be a means of doing less than full testing on a system that might require it. This is not the intention. The objective is that through a comprehensive impact assessment process, those systems presenting a risk to product quality are identified and given the attention appropriate to this level of risk, and by the right people (e.g. QA Departments).

For this process to work it is essential that an explicit rationale is provided for the impact assessment and that the rationales are fully understood, documented and endorsed by QA departments. This places a responsibility upon engineers to communicate clearly the nature of operation of engineering systems, and their potential impact on product quality.

Design for Impact

This term is used to describe the practice of making conscious design decisions with respect to the impact of the system in operation *at the beginning of design development*. By careful design, the number of systems capable of having a direct impact can be reduced; the direct impact *functions* remain but the systems with which they are associated are chosen by the designer.

Good Engineering Practice

Good Engineering Practice, commonly referred to as GEP, is proven and accepted, cost-effective, engineering methods and practices that ensure the effective satisfaction of stakeholder requirements. As such, GEP ensures that an engineering project meets the requirements of the user while being cost effective, compliant with regulations and well documented. Guidance and standards that have been defined by engineering institutes and other learned bodies support GEP. For direct impact systems, GEP is supplemented by *Qualification Practices* with the active participation of Quality Assurance personnel.

Enhanced Design Review

Enhanced Design Review[1] has been defined within the guide as:
A documented review of the design, at an appropriate stage in a project, for conformance to operational and regulatory expectations.

A structured review of the design of facilities, utilities and equipment is not an FDA demand (although draft European GMP requirements suggest that this could become a European requirement in the form of *Design Qualification* (DQ)).

However *Enhanced Design Review* (EDR) has been positioned in the Guide as the "smart" way to prepare for IQ and OQ. It is in the interests of all to reveal design or specification problems through a rigorous, structured review process early in a project rather than discover them later, where a remedy might involve significant delay and expense. However, with the exception of computer based systems, a structured and documented approach to assessing design, whether in the form of EDR or DQ, currently remains a business risk driven choice not a regulatory demand.

How should designs be assessed? There are many approaches (e.g. FMECA) however the rigor of the method by which the design is examined should be commensurate with:

- the impact of the system

- system complexity

- familiarity or degree of novelty with the system and-or the supplier

- the novelty of application i.e. standard equipment put to a new use

A familiar system of simple design with no impact on product quality should be subject to sufficient scrutiny during design development as part of Good Engineering Practice, and performance of an FMEA-type approach (for example) could be excessive in such circumstances.

Commissioning

The term *Commissioning* typically encompasses the following tasks:

- physical completion (a milestone)

- inspection

- setting-to-work

- regulation and adjustment

- testing and performance testing

- planning and preparation associated with managing the above activities

These terms and their associated tasks described within Codes of Practice etc. define GEP for commissioning and should form the foundations for Installation and Operational Qualification.

Qualification Practices

These are the general characteristics of a Qualification *regime* and include:

- active participation of Quality Assurance

- enhanced documentation, document management and a structured approval process

- QA change control

- greater end user participation

- use of Qualification Rationales to identify what should be checked, how, to what extent, why and by whom.

- deciding what <u>not</u> to check and why.

In line with the guide philosophy, *Commissioning* activities performed within such a regime would comprise IQ/OQ.

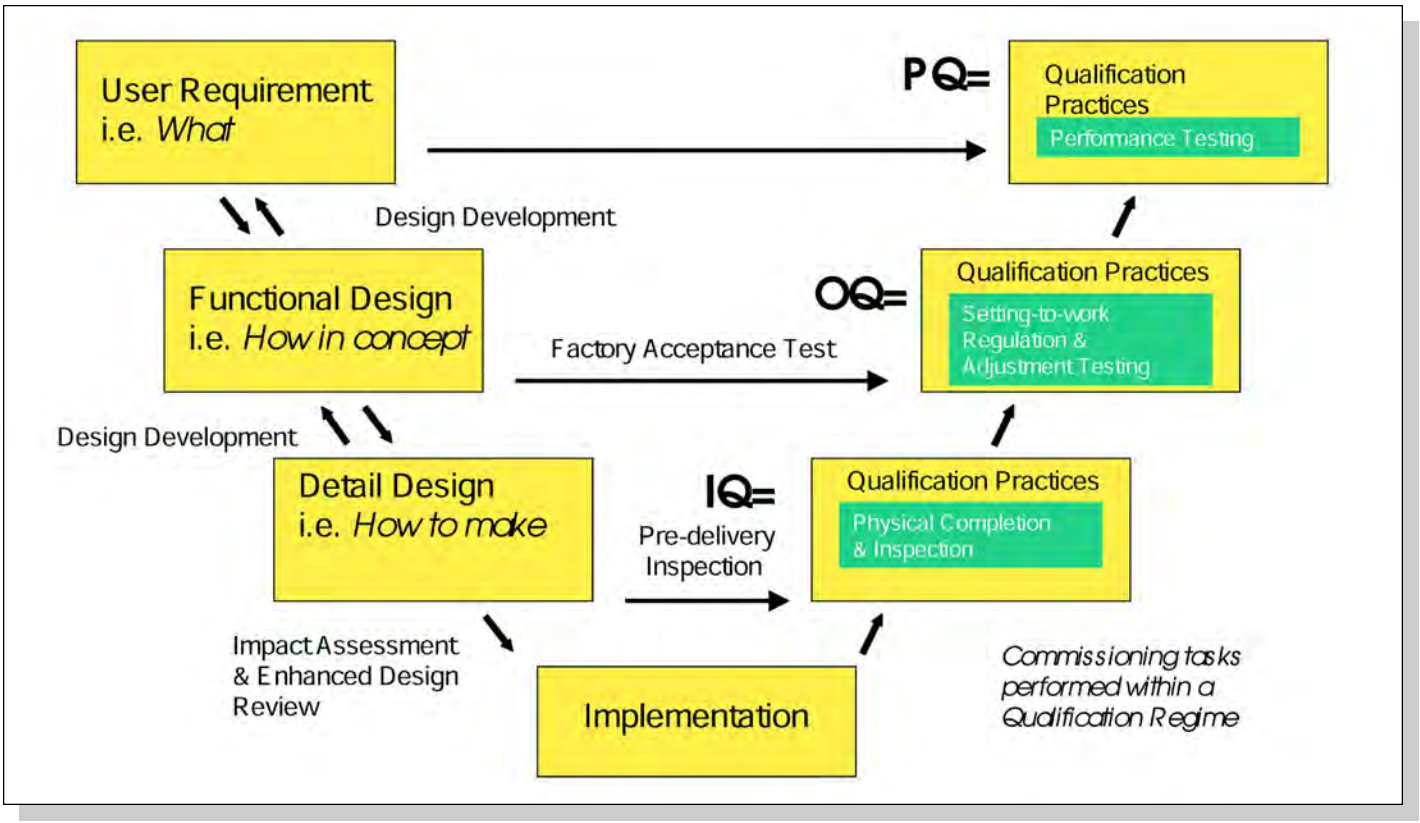

Figure 1.

Qualification Relationships - The V-Model

The V-Model is a simple and easily understood means of describing the relationship between the User Requirements and the designs and specifications prepared to meet them, and the levels of inspection and testing performed as part of Commissioning and Qualification.

Figure 1 illustrates the V-model for a Direct Impact System requiring Qualification; the Qualification tasks are equivalent to those described for commissioning but are supplemented by the more rigorous controls of Qualification Practices. The V-Model illustrates:

- To Commission or Qualify a system effectively, the performance, construction and operational requirements of a system should be known.
- PQ is used to verify the User Requirements.
- OQ verifies the functional requirements (of an individual system).
- IQ verifies the construction and installation.
- Factory Acceptance Tests are operational checks and these can and should contribute to the OQ where practical.
- Pre-delivery Inspection is a construction check and these can and should contribute to IQ where practical.

For some items of equipment, the construction and operation can be checked nearly completely at the supplier's works, leaving only the inspection associated with site installation, and the testing associated with integration with other systems. This is an opportunity to progress with IQ and OQ.

Build on the Potential Contributions of your Suppliers

The V-Model focuses on the basic lifecycle required by the end-user, however this neglects the contribution that could be made by the procedures, systems and documentation used and followed by a supplier or contractor. In many cases the supplier or contractor will have their own quality system (e.g. ISO 9001 parts 1-3) that demands a structured approach with equivalent relationships between Qualification tasks as represented by the V-model; in effect their own V-model. Where this is the case, the usual practices of the contractor or supplier can be integrated within the Qualification effort owned by the end-user.

The Role of Quality Assurance

The Quality Assurance department plays an essential role during the Commissioning and Qualification process. Although in the past Quality Assurance (QA) may not have been involved with Commissioning and Qualification until the later stages in a project, early involvement is being encouraged and promoted within the Guide as this will deliver the following benefits:

- An understanding from QA of the facility, processes and equipment well in advance of use for commercial manufacture
- QA can ensure commissioning activities are performed within a Qualification regime where they can support Qualification activities and eliminate duplication of effort.
- A partnership is established between Engineering and QA that ensures efficient hand-over for commercial start-up

Commissioning has traditionally been viewed as an engineering activity where QA involvement was unnecessary.

Summary

- *Good Engineering Practice* (including *Commissioning*) makes a significant contribution to meeting the regulatory demands of the pharmaceutical industry.

- GEP should be supplemented with *Qualification Practices* where systems have a *Direct Impact* on product quality.

- *Impact Assessment* must be supported by QA-endorsed rationales.

- How we choose to use some systems determines their *Impact* - design carefully with desired impact in mind.

- Adopt a multidisciplinary approach and encourage the early involvement of QA.

- The *Baseline*® approach is to design for *No or Indirect Impact* and only apply *Qualification Practices* to *Direct Impact Systems*.

Footnote

1. The Term "DQ" has not been used to avoid confusion between the FDA interest in the design of medical devices and that of facilities, utilities, and equipment.

Acknowledgements

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This article presents the results of a corrosion failure analysis conducted to establish the cause of corrosive pitting and the mode of failure for a biowaste spool piece.

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Biowaste Spool Piece Corrosion Failure Analysis Points to Chemical Makeup of 316L Stainless Steel

by Sunniva Collins

Introduction

A failure analysis conducted to establish the cause of corrosive pitting and the mode of failure for a biowaste spool piece revealed an important insight regarding system design. Results of the analysis suggest that base chemistries and thermal history play a significant role in the potential for ferrite formation in 316L stainless steel. These results indicate that the alloy makeup of 316L stainless steel used in the construction of a system will have a strong effect on how long the system will withstand a corrosive environment. Accordingly, the chemical makeup of 316L should be considered when designing systems for welded applications that experience corrosive service.

AISI 316L is commonly used in many industries, including the bioprocess or pharmaceutical industries, in fluid system applications. 316L stainless steel is mostly iron with significant alloying additions of chromium, which gives the metal its "stainless" or corrosion-resistant characteristics, and nickel, which stabilizes the austenite and makes the metal nonmagnetic and tough. In terms of performance, cost, and availability, this alloy is the optimum choice.

In bioprocess applications, large systems of AISI 316L tubing are orbitally/autogenously welded in place. As a method of construction, welding is fast and avoids the crevices (and potential for crevice corrosion) common with mechanical couplings. Unacceptable weld characteristics include bead meander, oxidation, and slag formation. There are also cosmetic geometric issues, such as weld bead width and height.

Cleaning in Place (CIP) is common in bioprocess applications. The systems must avoid corrosion in service as corrosion products will contaminate the final product. Bioprocess applications are usually wet, which introduces the possibility of rouging and microbially induced corrosion. Rouge is a contaminant found in many hot water and steam systems consisting of various forms of iron oxide; these iron oxides are a corrosion product that can affect the purity of the final product. Rouge is often treated by shutting down, cleaning, and repassivating the entire system. Microbially Induced Corrosion (MIC) initiates in the heat affected zones of welds, as well as in crevices or cracks. MIC occurs when aerobic and anaerobic microbes create a colony by removing material, forming deep pits with small pinhole openings on the interior of the tube. Presence of MIC in a system can speed up corrosive processes drastically; a system designed to work for 10 years can fail in two years or less if MIC is present.

Pitting corrosion is the most common failure mode in welded 316L, and therefore the mode of concern. Pitting is a form of localized attack caused by a breakdown in the thin passive oxide film that protects stainless steel from the corrosion process. Pits are commonly the results of a concentration cell established by a variation in solution composition in contact with the alloy.

Figure 1. Components in welded assembly.

Component	Description	Construction
1	0.5 in. long sanitary flange fitting	Machined from thick wall tubing
2	10 in. long tubing	Welded and drawn tubing
3	4.5 in. long tubular 90° elbow fitting	Hydroformed tubing
4	10.25 in. long tubing	Welded and drawn tubing
5	1.75 in. long sanitary flange fitting	Machined from thick wall tubing

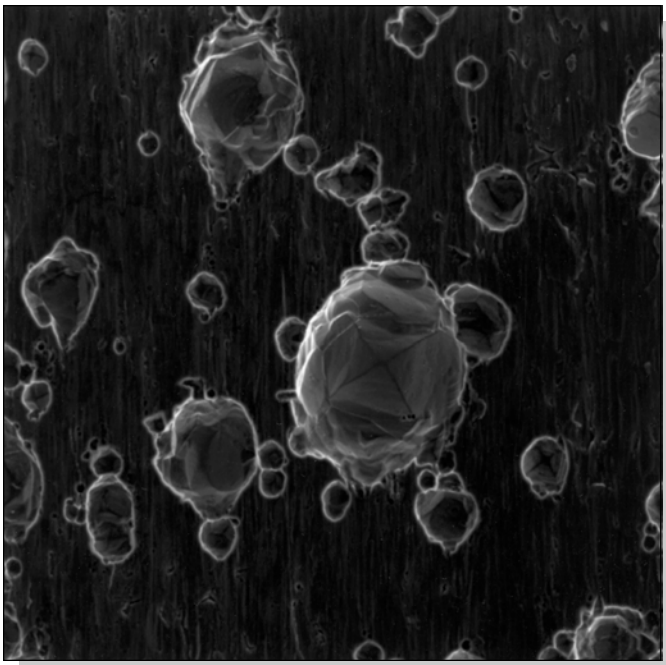

Figure 2. Pitting on #2 side of weld between components #2 and #3, approximately 5 mm from weld line at 2:00 position (near top of tube) on inside (wetted) surface. 500 ×. Note planar morphology of pits, indicating grain boundary attack. Accelerating voltage 20 keV, working distance 16 mm, condenser lens 3.01, secondary electron mode.

These variations occur when the solution at a surface irregularity (such as an inclusion) is different from that of the bulk solution composition. Once a pit has formed, it acts as an anode supported by a large cathodic region. Pits often nucleate at specific microstructural features in the weld deposit. In welded 316L, these features include d-ferrite in an austenite matrix, or microsegregation of alloying elements in the dendritic weld microstructure.

Background

A failure analysis was conducted on a biowaste spool piece consisting of a welded assembly, which showed evidence of corrosive attack - *Figure 1*. This failure was considered to be premature since the assembly had been in service for only about two years, as a piece of the transfer line between the collection vessel and a kill vessel in a bioprocess system. The system fluid was a dilute aqueous stream of salts, sugars, and proteins, operated at ambient pressure and temperature. The sample was steam-sterilized prior to shipment for analysis, but was not cleaned.

The five components of the assembly had been orbitally and autogenously welded together for a total of four welds; the weld beads appear to have been made using a manual TIG welding procedure. The interior surfaces of all four welds had discrete pitting concentrated at the 2 o'clock position on the side opposite to the direction of the weld. In addition, there were two bands of haze on either side of each weld, approximately 2.5 mm from the edge of the weld bead. A discolored ring was visible, approximately 10 mm from the edge of the weld bead, on the interior surfaces of Components #2 and #4. Isolated pinpoint pits were evident on the interior and exterior surfaces near the second weld (Component #2) at the 6 o'clock position.

The spool piece was in service in a horizontal position. The top and bottom of each weld was identified, and a distinct difference was noted in the corrosive pitting between the two halves. The top had many pits and a brown residue. The bottom had a few larger pits and no noticeable residue.

Failure occurred due to corrosive pitting that breached the wall thickness of a welded and drawn tubing component (Component #2), approximately 10 mm from the edge of the weld of a tubular elbow fitting (Component #3), at the 6 o'clock (bottom) position. The failure was located at the intersection of the Heat-Affected Zones (HAZs) of the orbital weld and the seam weld in Component #2.

The following sections outline the analytical procedure, test results, and possible causes for corrosion and failure.

Analytical Procedure

A complete metallurgical analysis was performed to establish the mode of failure and to determine whether other measures could be taken to avoid premature failure by corrosion. The following procedures were followed:

- Document the assembly as received with photographs and measurements; make a scale drawing of the assembly.
- Measure ferrite content in welds with a ferrite indicator and a Ferritscope; measure magnetic permeability μ with a magnetic permeability indicator.
- Section assembly into five component parts and four weld parts.
- Perform SpectroChemical Analysis (SCA) on samples of the five component parts to determine elemental makeup of the 316L stainless steel.
- Perform roughness readings on the five component parts

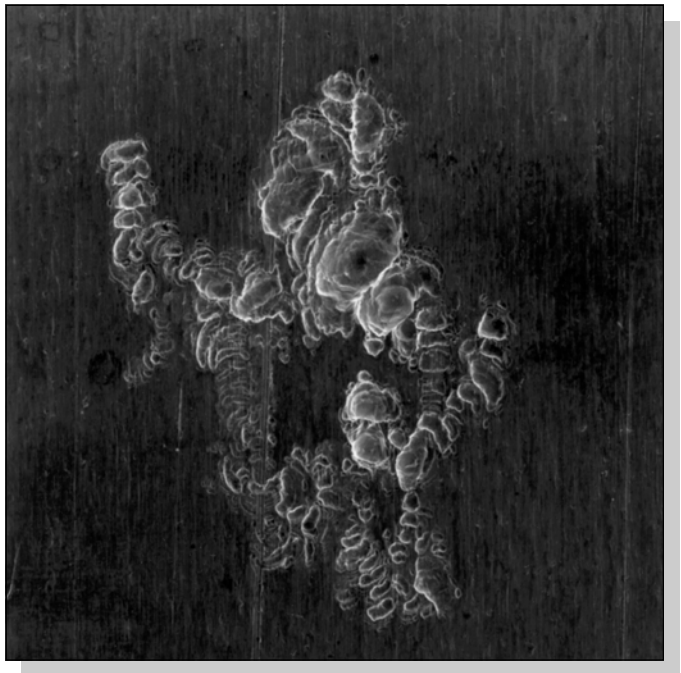

Figure 3. Pitting on #2 side of weld between components #2 and #3, approximately 5 mm from weld line at 6:00 position (at bottom of tube) on inside (wetted) surface. 80 ×. Pinholes leading to larger subsurface cavities are visible. Accelerating voltage 20 keV, working distance 17 mm, condenser lens 3.01, secondary electron mode.

Surface roughness as measured using contact profilometry*				
	Component 2	Component 3	Component 4	Component 5
Ra max, µin.	8	13	8	7
Ra ave, µin.	8	3	7	3
Ra min, µin.	7	3	6	2
Key measurements from surface analyses depth profiles				
Oxide thickness, Å	54	40	62	47
Max Cr/Fe ratio (Depth, Å)	1.8, 17	1.7, 12.5	1.9, 22	2.5, 17
Cr enrichment layer thickness, Å	34	27	44	38
Carbon layer thickness, Å	13	16	25	11
* Cutoff, 0.03 in.; Drive speed, 0.01 in./s; Traverse length, 0.574 in.				

Table A. Surface measurements.

using a surface analyzer (contact profilometer).

- Evaluate the passive wetted surfaces of the component parts using Electron Spectroscopy for Chemical Analysis (ESCA) and Auger Electron Spectroscopy (AES).
- Perform Scanning Electron Microscopy (SEM) on areas of interest.
- Section, mount, and polish longitudinal specimens from the five component parts and the four welds; examine unetched microstructure for inclusions; etch and evaluate grain size; perform microhardness tests using an indenter and a 500 g load.

Results and Discussion

SEM was performed on the areas of interest in both the secondary and backscatter electron modes. SEM micrographs in secondary electron mode offer the best resolution, produce an abundant signal, and permit viewing of the areas of the specimen that are not in a direct line of sight with the collector. SEM micrographs in backscatter electron mode improve image contrast, especially with smooth specimens and at low magnifications. The backscattered electron mode is useful for determining local differences in chemical makeup.

The SEM micrographs of Component #2 show that pitting at the top and bottom of the assembly differs significantly. The pits near the top of the tube are not deep and appear to be due to grain boundary attack that removes an entire grain of material from the surface, indicated by the planar surfaces within the pits - *Figure 2*. The pits are distributed on the surface in a relatively even fashion, and material removal does not appear to be more than one grain deep. It is possible that this area was over an air pocket, as grain boundary attack would be more likely in contact with a vapor phase. EDS analysis of a thin non-adherent surface oxide residue showed evidence of enrichment in iron and oxygen.

Pitting attack also occurred at the bottom of the tube—on both the interior and exterior of the tubing. At low magnifications (under 100x), the morphology of these pits (pinhole surface openings leading to large subsurface cavities) indicated that Microbially Induced Corrosion (MIC) could be postulated as a potential failure mode - *Figure 3*.

The interior (wetted) surface of the tubing shows a surface with *some* of the characteristic indicators of MIC. For example, the many clustered pits indicate an area of adhesion for a corrosive deposit, and the pinholes lead to larger cavities. These characteristics are typical of MIC, which depends on the interaction of aerobic and anaerobic bacteria; typically the aerobic bacteria create a deposit first, and the anaerobic bacteria thrive under this deposit. However, some of the key indicators of MIC were *not* present, such as ordered elevated sulfur levels, substructures of silicon, calcium, and oxygen, or spheres consisting of iron and oxygen. Based on the absence of these indicators, MIC is not verified as the failure mode.

The surface chemistry analyses were performed using Auger Electron Spectroscopy (AES) and Electron Spectroscopy for Chemical Analysis (ESCA). Auger is used to evaluate the composition and thickness of the oxide layer, and the depth at which the maximum Cr/Fe ratio occurs. The Cr/Fe ratio is a

	Seam welds		Orbital welds between components			
	2	4	1 and 2	2 and 3	3 and 4	4 and 5
X ave	1.06	1.08	4.09	4.57	4.45	4.03
X min	0.43	0.95	3.45	3.84	3.94	3.34
X max	1.32	1.26	4.69	5.14	4.81	5.26
S, Standard Deviation	0.27	0.11	0.45	0.39	0.23	0.60
N, sample size	10	10	10	10	10	10

Table B. Percent ferrite content of welds as measured using a Fisher Ferritscope.

	Component 1	Component 2	Component 3	Component 4	Component 5	316L
Ni	10.99	10.17	12.27	10.20	12.14	10.00-14.00
Mn	1.96	1.86	1.31	1.86	1.81	2.00 max
C	0.026	0.014	0.018	0.017	0.02	0.030 max
N	0.079	0.053	0.055	0.054	0.072	0.10 max
Cu	0.29	0.28	0.073	0.29	0.27	NR
Ni eq.[1]	13.58	12.09	13.92	12.21	14.43	10.00-16.70
Cr	16.73	16.88	17.66	16.87	17.18	16.00-18.00
Mo	2.26	2.08	2.12	2.08	2.35	2.00-3.00
Si	0.42	0.36	0.57	0.35	0.46	0.75 max
Nb	0.01	0.012	0.018	0.012	0.006	NR
Ti	0.002	0.003	0.002	0.001	0.002	NR
Cr eq.[2]	20.48	20.30	21.46	20.27	21.11	18.74-23.23
Cr eq./Ni eq.[3]	1.51	1.68	1.54	1.66	1.46	1.12-2.32
P	0.038	0.02	0.016	0.02	0.01	0.030 max
S	0.017	0.019	0.018	0.02	0.001	0.030 max
Al	0.02	0.01	0.01	0.01	0.013	NR
O	0.0044	0.0035	0.0044	0.0037	0.0031	NR
Co	0.10	0.13	0.05	0.13	0.05	NR

[1] Cr equivalent = Cr + 1.37 Mo + 1.5 Si + 2 Nb + 3 Ti; all values in weight percent.

[2] Ni equivalent = Ni + 0.31 Mn + 22 C + 14.2 N + Cu; all values in weight percent.

[3] At values of Cr eq/Ni eq below 1.5, the solidification mode is austenitic or austenitic-ferritic, which corresponds to a cosmetically unacceptable weld. For values of Cr eq/Ni eq between 1.5 and 2.0, the solidification mode is ferritic-austenitic. Welds with this solidification mode are acceptable. However, the higher the number is, the higher the propensity for the formation of ferrite.

Table C. Spectrochemical Analyses of Components (elemental values in Wt. %).

measure of the chromium enrichment in the passive oxide film. It is defined as the maximum ratio of chromium to iron within the oxide layer. The depth of enrichment is the location within the oxide layer where Cr/Fe equals 1. The oxide thickness is defined as the depth at which the Full Width Half Maximum (FWHM) of the oxygen peak occurs. ESCA is used to determine the quantitative surface composition including contaminants. ESCA provides information on chemical makeup and on the nature of the chemical bonds as well. The total Cr/Fe ratio is defined as the relative concentration of Cr and Fe within approximately the outer 50Å. This measure includes Cr and Fe in oxide and metallic states, and also indicates the relative chromium enrichment in the passive layer. The CrO/FeO ratio is the ratio of Cr in the oxide state to Fe in the oxide state.

The ESCA and AES analyses provided no unusual findings. Samples were taken from representative non-corroded areas to ascertain whether there were differences in the surface oxide chemistries and thicknesses that would contribute to corrosion initiation. The oxide thicknesses, oxide compositions, and maximum Cr/Fe ratios are representative of results from electropolished and passivated 316L stainless steel surfaces. The Cr/Fe value of the samples ranged from 1.5 at 17Å to 2.5 at 17Å . The oxide layers ranged from 40 Å to 62 Å. The surface carbon thickness of the samples ranged from 11 Å to 25 Å. The chromium depth enrichment of samples ranged from 27 to 44 Å - *Table A*. Elemental surveys of the surfaces display elements associated with stainless steel as well as typical process contaminants, which include silicon, sulfur, phosphorous, carbon, nitrogen, and contaminants indicative of handling (potassium, calcium, and sodium). *Note: Surface roughness data and surface chemistry (ESCA and AES) results are not available for Component #1. Once samples were taken for spectrochemical analysis to determine base chemistry and for metallographic mounts to examine microstructure, there was no material remaining for these other test methods. Spectrochemical analysis is a destructive method that requires at least 50 g of material. However, since Component #1 did not participate in the failure and it appeared relatively unaffected by its exposure, it was determined that chemical makeup and microstructure were sufficient information.*

In addition, surface roughness readings showed no significant differences. All components had average surface roughness under 10 µin. These measurements also indicate smooth, electropolished surfaces.

Of particular interest in this failure is that only the welded and drawn tubing components (Components #2 and #4) show any evidence of corrosive attack—and only in the vicinity of the weld. In fact, the other components looked as good as new and probably could have continued to function. Based on the chemistries and microstructures of Components #2 and #4, it can be assumed that they came from the same heat of tubing. An optical metallographically prepared surface etched to reveal grain size reveals a variation in grain size between the surface and the interior. This microstructure, with larger grains

at the surfaces and finer grains in the interior, occurs when a worked part is not annealed completely.

The measurable ferrite in the seam welds of both components also indicates an incomplete anneal, which may mark a higher propensity for failure. The failure was located at the intersection of the Heat-Affected Zones (HAZs) of the orbital weld and the seam weld in Component #2. The average ferrite content was measured using a Ferritscope. At this location, average ferrite content was 4.57 %, the highest ferrite content in the entire assembly - *Table B*.

The Difference is Chemical Makeup

Components #2 and #4 differed from the other components in chemical makeup - *Table C*. Minor changes in the chemistries of 316L stainless steel can alter the way the alloy solidifies during welding. Possible solidification modes for 316L include *austenitic*, *austenitic-ferritic*, *or ferritic-austenitic*.

- The *austenitic* weld solidifies completely as austenite and no further high-temperature transformations occur.
- The *austenitic-ferritic* weld solidifies as austenite, and delta ferrite is formed from the melt retained between the austenite dendrites.
- In the *ferritic-austenitic* weld, ferrite solidifies first and austenite forms between the ferrite dendrites. The austenite subsequently grows into the ferrite, resulting in a significant decrease in the volume fraction of the ferrite. At room temperature, the weld is substantially austenite with a small volume of retained ferrite.

The competition between ferrite-promoting elements and austenite-promoting elements can be described by the chromium and nickel equivalents. The chromium equivalent takes into account those elements that promote the formation of ferrite, which is the stable bcc form of iron. The nickel equivalent accounts for those elements that promote the formation of austenite, the metastable fcc form of iron. In austenitic stainless steels, there must be enough chromium present to form the stable chromic oxide layer (which gives the steel its stainless characteristics) balanced by enough austenite forming elements to stabilize the crystal structure as austenite. There are several commonly used chromium and nickel equivalents, but the equations developed by Hammar and Svensson[1] show an excellent correlation between composition and solidification mode, especially for austenitic stainless steels. (All values in weight percent.)

Cr eq = Cr + 1.37 Mo + 1.5 Si + 2 Nb + 3 Ti, and
Ni eq = Ni + 0.31 Mn + 22 C + 14.2 N + Cu

Using these equations, solidification mode can be predicted by the ratio of Cr eq/Ni eq.[2] At values of Cr eq/Ni eq below 1.5, the solidification mode is austenitic or austenitic-ferritic, which corresponds to a cosmetically unacceptable weld. For values of Cr eq/Ni eq between 1.5 and 2.0, the solidification mode is ferritic-austenitic. Welds with this solidification mode appear to be acceptable. However, the higher this number is, the higher the propensity for the formation of ferrite in an orbital autogenous weld.[3] Welding technique may have some effect on the solidification mode since it can affect the weld metal composition through dilution and nitrogen pickup. However, for the relatively small and precise welds common in autogenous welding for higher purity applications, the overall effect of solidification conditions is of secondary importance, and solidification mode is largely determined by chemistry.[4] Under practical solidification conditions, the transition between austenitic-ferritic and ferritic-austenitic solidification modes occurs when Cr eq/Ni eq = 1.5 ± 0.03.

As Cr eq/Ni eq increases, the higher the propensity for the formation of ferrite. A small amount of d-ferrite reduces the tendency for hot cracking when 316L is welded.[5,6] However, the presence of d-ferrite in welded austenitic stainless steel has been found to stimulate pitting corrosion,[7] and recent specifications indicate a very low allowable d-ferrite for use of welded components in corrosive service.[8] Current research indicates that corrosion resistance is significantly affected in orbitally welded 316L when delta ferrite exceeds 3% in the weld.[9]
At ratios of 1.68 and 1.66, Components #2 and #4 are well above the ratios of 1.45 to 1.54 for the other three components. *The high Cr eq/Ni eq values, combined with the incomplete anneal and the thermal excursion caused by the welding, increases the tendency for the formation of ferrite.*

Conclusions

Failure occurred due to corrosive pitting that breached the wall thickness of welded and drawn tubing (Component #2), approximately 10 mm from the edge of the weld with Component #3, at the 6 o'clock position. The seam weld of Component #2 had been bead reduced, but had not been fully annealed, as shown by a ferrite indication along the seam and the duplex grain size of the microstructure. The orbital weld connecting the tubing and the elbow fitting (Components #2 and #3) intersected with the seam weld of the tubing (Component #2) at the 6 o'clock position, resulting in a localized ferrite content in excess of 4.5 %. This localized microstructure, in combination with the aqueous environment and time of exposure, provided the necessary and sufficient conditions for corrosive failure to occur. Only Components #2 and #4 showed any evidence of corrosive attack, and only in the vicinity of the weld.

Chemistries and thermal history will impact the potential for ferrite formation in 316L, which in turn affects corrosion resistance. This finding is particularly important in welded applications in corrosive service. As illustrated by this failure, piping systems in bioprocess applications are often constructed of different heats of 316L with significant variations in composition. In the welded condition, some of these heats will have more retained ferrite, and can experience premature failure due to corrosion. The Cr eq/Ni eq can be used to evaluate the effects of the material composition on ferrite formation. Keeping ferrite under 3% in orbital welds can improve system performance, reduce the potential for corrosion byproduct contamination, and reduce downtime for emergency system maintenance.

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This article presents future opportunities and challenges for the pharmaceutical industry that arise from the human genome effort.

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Productivity in Pharmaceutical Research and Development

by Michael R. Pavia

The information obtained from the sequencing of the human genome is affording the pharmaceutical industry a huge opportunity; however, the industry also faces enormous challenges due to lack of productivity. To take maximal advantage of these opportunities, the drug discovery and development process must be redefined by increasing the probability of success, reducing the time to market, and introducing truly personalized medicine. These approaches will fuel future innovation and ultimately change the current practice of medicine.

The year 2000 represents a very important year for the pharmaceutical industry. This was the year the sequence of the human genome was completed. In fact, future generations may very well look back years from now and remember this year and this event as the most significant in the history of human healthcare.

The information supplied within the human genome represents a foundation for tremendous progress and opportunity in medicine-from new targets for improved therapeutics to truly personalized medicine. When the revolution in electronic communication is included, it is not hard to imagine the practice of medicine being radically different then it is today. The beneficiaries of this radical change will be the entire human race.

This article will discuss two of the pharmaceutical industry's greatest opportunities for the next decade that arise directly or indirectly from the genome effort, as well as the associated challenges. These two areas are 1) the use of new high-throughput technologies to radically improve the productivity of the pharmaceutical discovery and development process, and 2) personalized medicine.

Productivity

It is a well-publicized fact that all of the drugs introduced to the market over the entire history of the pharmaceutical industry act upon less than 500 unique gene products. The completed sequence of the human genome is expected to contain approximately 30,000 genes.[1] Conservative estimates place the number of new targets for drug discovery at about 10% of this total, or about 3,000. Therefore, it is expected that the pharmaceutical industry will have a huge wealth of new targets for therapeutic intervention.

But herein lies the challenge: it can be argued that the productivity of the current pharmaceutical discovery and development process will not allow the industry to adequately recognize the benefits of this genome information in a timely fashion. In addition, the current economics of the process (detailed below) jeopar-

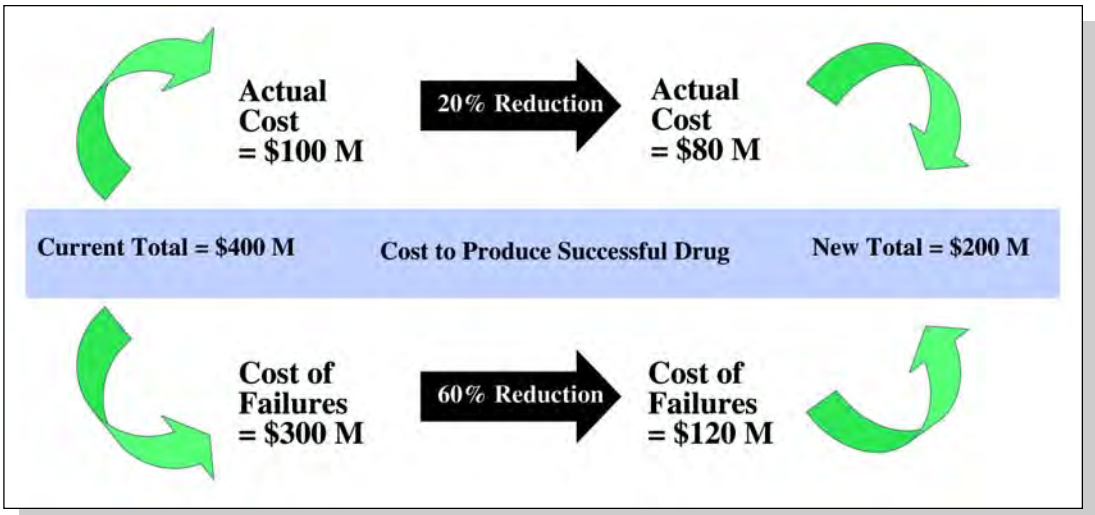

Figure 1. 100% productivity improvement in the drug discovery and development process.

dize the future of the pharmaceutical industry itself. Some facts: the average new drug costs in excess of $400 million to discover and develop (some estimates range as high as $1 billion) and takes 10-12 years to reach the marketplace.[2] And the trend is for new drugs to become even more expensive to develop in the future. Secondly, to achieve respectable returns to investors, a major pharmaceutical company needs to introduce 3-4 significant new chemical entities to the market per year. This simply is not happening. If anything, it appears industry-wide productivity is declining. In 1988, global research spending of $15 billion produced a little more than 50 new drugs. Ten years later global research spending of $35 billion (in inflation adjusted dollars) produced a little more than 30 new drugs. Using today's traditional process of identifying targets and developing drugs, the industry has a major productivity problem which may threaten its existence.[3,4]

Now compound this issue with the challenge of taking advantage of the thousands of gene products in the human genome that may represent viable targets for the pharmaceutical industry. The pharmaceutical industry needs to find methods to discover and develop new drugs in a more productive manner.

To address this industry-wide problem, the industry must undertake a major program with the goal of increasing the productivity of the pharmaceutical discovery and development process by at least 100% over the next several years. Key to the success of this initiative for increasing productivity throughout the pharmaceutical industry is the intelligent application and integration of novel high-throughput technologies to the discovery and development process. These novel technologies must be applied to every part of the process from gene discovery to patient care to develop breakthrough healthcare products in a much more productive fashion.

To determine how to address the industry's productivity problem, it is important to examine the reasons why drug discovery and development is such an expensive process. It has been estimated that approximately 75% of the total cost of a new drug is spent on compounds that fail somewhere in the process.[5] For example, it is not uncommon to select a target for drug discovery and only find out that the target is unsuitable during late-stage clinical development. The company must return to the very beginning of the process when this occurs. Using today's processes, less than 1 in 25 new molecular targets and less than 1 in 5 drugs that enter clinical trials make it to the market. So, the majority of productivity increases can be realized by reducing failures, especially failures that occur late in the development process. However, there also are significant productivity increases to be had by optimizing the process for the successful candidate by, for example, focusing on optimized workflow and decision making processes. So, how can we achieve 100% productivity increases? In Figure 1, the average cost of discovering and developing a new drug is $400 million. Approximately $300 million is the cost applied to projects that fail. If the cost of failures can be reduced by 60%, this would bring the cost of failures to $120 million. A 20% reduction in the cost of discovering and developing the successful drug can be achieved. This reduces its cost from the historical $100 million to $80 million. Therefore, the total average cost would be $120 million + $80 million = $200 million, a 100% improvement in the starting point of $400 million.

This article will discuss ways to achieve reduction in the cost of failures. After a detailed study of the major causes for failure in the process, there are three major areas where reduction in failure rate would achieve the greatest increase in the productivity of the discovery/development process. These

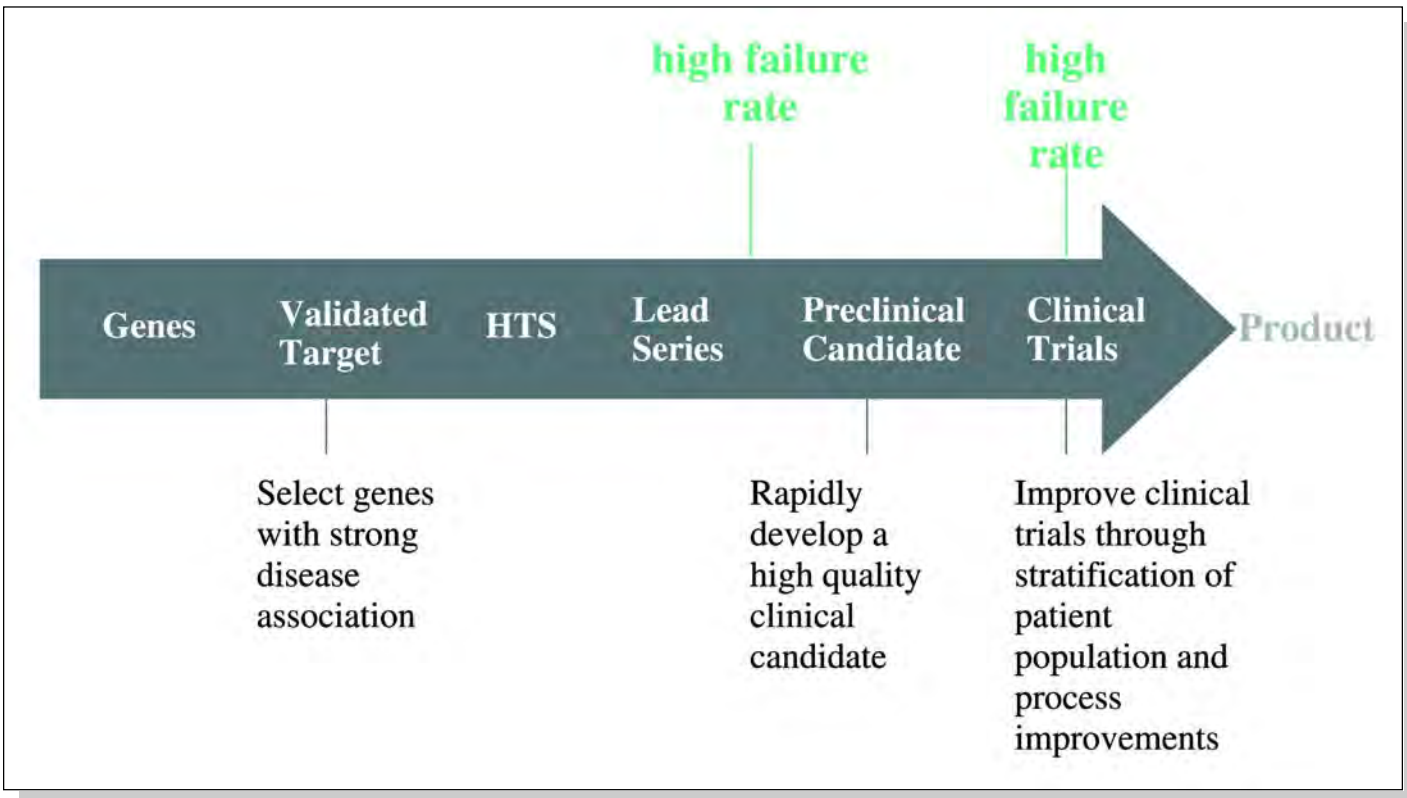

Figure 2. Improving productivity - where to Focus?

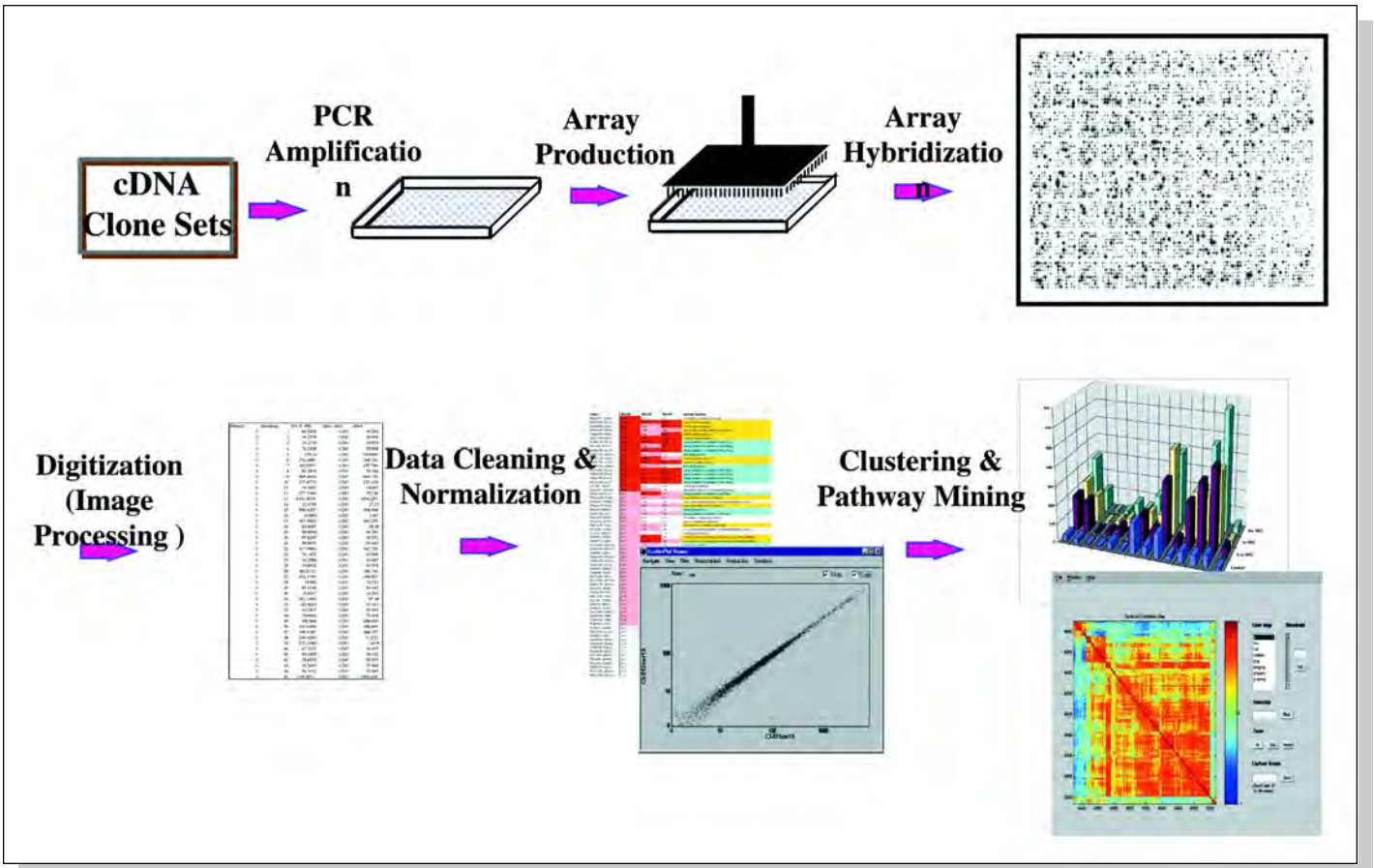

Figure 3. Transcriptional profiling (mRNA).

areas are target validation, late lead selection, and clinical trials-Figure 2. Each of these are discussed in more detail.

Target Validation/Functional Genomics

Much has been written about sequencing the human genome. Obtaining this sequence information is now fairly routine. The next great challenge is using this information to select useful targets for drug discovery. While certain genes may already be implicated in a disease or a biological trait of interest, more commonly, significant additional study is required to establish the specific functions of these genes and the roles they play in the disease of interest. The process of ascribing biological function to genes is known as target validation/functional genomics and requires demonstration that modulation of the function of the putative target gene (or its product) is likely to have a beneficial therapeutic effect. Such confidence means that the chance of failure in clinical trials due to lack of efficacy will be significantly reduced.

While there are many different approaches to target validation within the industry, the following discussion presents an example to illustrate one approach to the problem. The first step in this process takes advantage of high throughput expression profiling experiments[6] (described in more detail below) which allow for the rapid understanding of which genes are turned on or off in a particular experimental paradigm. While this is an exciting new technology which holds great promise in drug discovery, it must be remembered that expression profiling experiments are only a crucial first step in target validation/functional genomics. One must be cautious in interpreting the data and must be sure that these results are coupled with further experiments to better associate the genotype with the phenotype in living organisms. If this association is not made, there is a risk of performing dysfunctional genomics.

Expression Profiling

Genetic messages and their encoded proteins modulate development, growth, disease, and death. The pattern of expression of a newly discovered gene, where and when it is formed, in which cells and tissues, and under what circumstances, provides vital clues to the function of that gene. Microarray-based expression profiling technology (Figure 3) allows scientists to simultaneously monitor the expression of tens of thousands of genes in a single experiment, providing a detailed view of the cellular circuitry by expression monitoring at the level of the whole genome. The power of this technique is in its scope: scientists can investigate differences between, for example, normal and malignant tissue, identify novel drug targets and genetic markers, elucidate specific genetic pathways regulated by a given drug, and determine the function of novel genes. At this point, it makes sense to centralize these high-throughput techniques into a core facility, to exploit economy of scale and emphasize rapid, high-quality, high-volume production. All data from these experiments should be stored in a central database and then analyzed with a suite of sophisticated software methods and tools to facilitate rapid and complex analyses-Figure 4.

But remember, expression profiling experiments are only a crucial first step in target validation/functional genomics. Further experiments must be carried out to better associate the genotype (the information at the gene level) with the

phenotype (what we observe with our eyes) in living organisms. This requires the capability to examine gene expression in appropriate animal and cellular models. A number of technologies are employed in these biological systems in order to up- or down-regulate a specific gene or gene product to determine whether or not a therapeutic effect can be achieved. For example, increasing the functional activity of a gene can be achieved by over-expressing a gene of interest in either a cell culture system or a whole animal. To over-express the gene, additional copies of that gene may be added to the DNA of the model cell system or animal model through the use of techniques such as plasmid DNA vectors, DNA injection, and retroviral vectors. Scientists can analyze the effects of over-expression of a gene in cell culture systems to elucidate the cellular role of a gene product; similarly, they can analyze the more complex, physiological effects of overexpression in transgenic mice.

Alternatively, the role of a gene can be elucidated by decreasing the functional activity of a gene (gene knock-down) or entirely removing the gene (gene knockout) from a cell or animal. Methods of reducing gene expression in cell culture systems include the use of antisense technology to decrease the formation of a specific gene, as well as the use of antibodies which inhibit function by binding to the protein of interest. In animal models, gene knock-out/knock-down models are created by knocking out the gene in embryonic cells to create whole animal models, by altering the on/off switch which regulates the expression of the gene at later stages of development, or by introducing additional copies of a gene containing different regulatory sequences to turn the gene on and off in very specific time frames or tissue type. Observation of changes in development, viability, behavior, and life span of these animals frequently provide important clues as to the gene's function and its role in complex disease processes. By using these animal models in high throughput screening assays, it is possible to identify potential drug compounds rapidly and cost-effectively. These biological systems and tools allow scientists to discover and investigate novel genes and their function in multiple disease processes. In addition, careful analysis of the results from this series of experiments help scientists in selecting those targets which should have the best chance of success in modulating disease in human clinical trials.

Late Lead Selection

In the process used by most of the industry today, a novel biological target is used to identify a compound that potently modulates that target. The structure of that compound is then modified to optimize the potency against that target. The next step is to further modify the structure of the compound to afford suitable properties for drug development. These properties include desirable absorption, metabolism, and toxicity properties (traditionally referred to as ADMET for absorption, distribution, metabolism, excretion, and toxicology). Many drug candidates fail in the latter stages of this process because a suitable structure can not be identified that simultaneously possesses all the desired properties.[7] In fact, 41% of drugs fail because of poor biopharmaceutical properties (stability, solubility, membrane permeability, metabolic liability, efflux, protein binding, etc). An additional 22% of drugs fail because they are toxic- Figure 5. Many of the technologies developed as part of the genomics revolution such as high throughput analytical processes, high volume expression profiling, and proteomics (the study of protein content) can be utilized to assess these properties early in a compound's development. Industry efforts to deliver the tools to build accurate *in vitro* surrogate measures of ADMET characteristics and associated computational methods should allow us to reduce the failure rate significantly or at least identify these failures much earlier in the process. These methods when incorporated into an automated industrialized process should significantly improve a compound's clinical trial success rate and reduce the overall costs.

Clinical Trials

In the area of clinical trials, there are two very large opportunities for productivity increases. The first is in the selection of patients for clinical trials; selection of patients that will optimize the chance of a successful outcome of the trial itself. This area will be discussed in more detail in the Personalized Medicine section. The second area is in optimizing the process of clinical trial design and management. This will be discussed more fully in the Process Optimization section which follows.

Process Optimization

Now, how can the 20% cost reduction be achieved for the successful drug mentioned earlier. The industry needs to apply the concept of process optimization across the entire gene-to-patient continuum. A very important question that the industry must consider is "can the pharmaceutical industry learn some lessons from traditional manufacturing companies?" The answer is clearly "yes." This means studying the discovery and development process from the perspective of a process engineer; the entire gene-to-patient process as a unified process where genes go in at the beginning and drugs come out at the end. By studying the process as one single piece, one can achieve a much greater understanding of where to best make process improvements. One must realize that just because you can carry out a specific assay faster doesn't mean you'll improve the whole process. One must identify bottlenecks and predict the expected effect of applying technologies such as automation to these bottlenecks. The next step is matching product flows throughout the pipeline so that resources are appropriately allocated. Finally, couple these predictive tools with a measurement system. This entire system lets employees ask how a potential improvement to the process will affect the entire process. Then when these improvements are carried out the scientist has the tools to see if the prediction was correct. This affords the ability to make constant real-time adjustments to productivity improvements.

Two possible initial focus areas: The first is supply chain management and the other is the clinical trial process. Typically, when a scientist plans an experiment they determine what reagents they'll need, order them, and then wait. If science is being done on an industrial scale then why not set up just-in-time supply of reagents. That way, as a drug progresses through the process the purchase order has already been placed automatically with the supplier and the experiment can be done immediately. Couple this effort with better design of experiments and better decision processes (which are the really crucial experiments that lead to the decision to proceed or kill a project) and the productivity enhancements can be dramatic.

A key area that is ripe for process improvements is clinical trials. Traditional clinical research processes are time consuming and costly, representing the majority of time and cost in the drug discovery and development process.

There is an enormous opportunity to move the clinical development process from a primarily paper based system to an electronic research system[8] which will streamline research

transaction processing, lower the associated cost per transaction, and markedly improve quality by access to real time data. Today, much of the transaction processing associated with clinical research is performed through batch data entry of paper case report forms that are delivered to a pharmaceutical company's central data management facility. Data is double entered for verification and then edited, resulting in queries that are mailed to the investigators for resolution. An obvious route for significant productivity gains will be through applying web-based clinical trial management from external clinical investigators directly to the pharmaceutical companies to more quickly allow data collection and confirmation from clinical investigation sites and allow more rapid data analysis.

Another significant area for process improvement is in clinical trial patient enrollment. Currently, most patients are identified by clinical investigators from their patient network. This type of patient enrollment is often one of the most time consuming steps in the clinical development process. The internet once again affords a potential opportunity to increase productivity. An increasing number of patients are routinely accessing disease information at home through the internet. Efforts are underway to link patient enrollment to these information sites. It can be expected that these efforts will result in quicker patient enrollment into clinical trials.

An additional opportunity to increase the productivity of the clinical development process is by using informatics and associated computational tools to design more effective clinical development programs.[9] Today, the average drug goes through 68 separate clinical trials. Using computational tools to run simulations of clinical trials can result in better clinical trial design and a decreased number of clinical trials that must be run.

Informatics

Another area that will contribute to significant productivity increases is the increased use of informatics. The high throughput processes discussed above generate very large quantities of information which must be collected, stored, analyzed, and mined. For example, a single expression profiling experiment can result in hundreds of thousands of data points. Informatics involves building and deploying tools that allow researchers to extract value from masses of data to design better experiments (e.g. designing disease-targeted arrays, clustering expression profiling data, mining genes, cross-database queries), and to rapidly analyze results and carry information to the next step. This activity involves representing data, looking for patterns in that data, and suggesting ways to proceed.

Essential components of informatics include databases

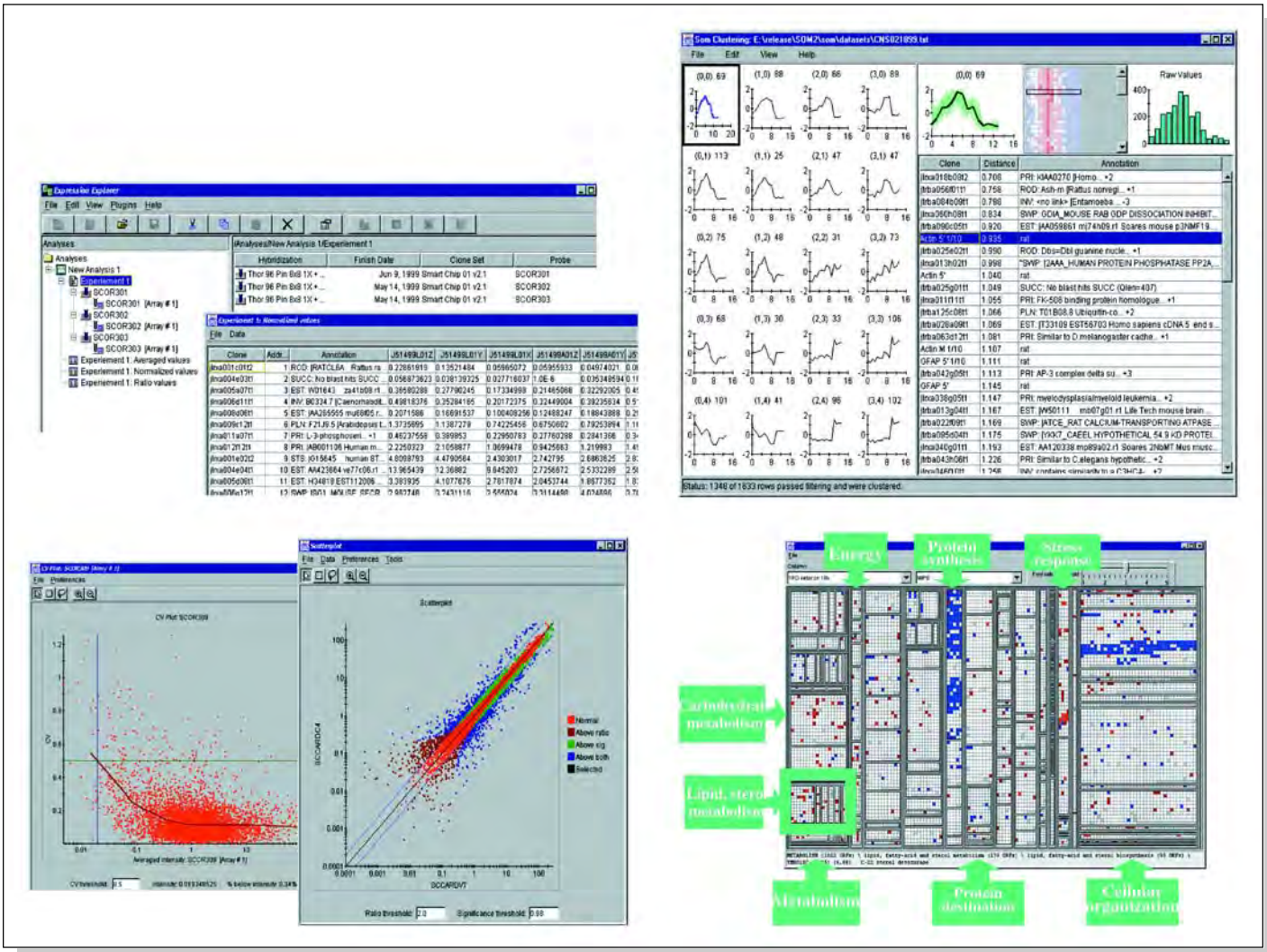

Figure 4. Analysis tools.

that store data, tools that allow queries across such databases, and mechanisms to collect and organize scientific annotations including the results of target validation, lead discovery, and clinical trials. It also includes applications that allow scientists to analyze their data (e.g. software for sequence analysis, transcription profiling, annotating proteins with their functions). The industry is continuing to expand its informatics base with new tools, databases, algorithms, and decision-support systems. An illustrative example of the new informatics tools being utilized are Self-Organizing Maps (SOMs) developed at the Whitehead Institute-Figure 4. These tools allow scientists to identify genes which are co-regulated and to visualize gene expression profiles based on mechanism of action. To achieve maximal value from the wealth of information at our disposal, the industry needs to increasingly focus its efforts on knowledge management. This means making the data and analyses from each of these high-throughput technologies available to all of our scientists to allow them to make decisions based on the maximum data with the minimum effort.

Finally, a key point about collaboration and integration. No one company alone can develop all of the new technologies to solve the productivity challenge. It is very important to constantly scour the world for useful new technologies, access these technologies, and most importantly, effectively integrate them into the discovery and development process. Of course, it should go without saying that the process platform utilized by any company must allow for rapid integration of these new technologies.

By focusing on reducing late stage failures through the judicious application of novel high-throughput technologies, process optimization, and addressing the information challenges, the industry should be able to achieve 100% productivity increases.

Personalized Medicine

The vast quantity of information from the human genome will not only transform the industry's ability to develop revolutionary pharmaceutical products, but also will profoundly influence the way in which medicine is practiced in the years to come. The industry is developing products that will bring this molecular information to the drug discovery and development process as well as directly to the patient to afford truly personalized medicine-Figure 6.

Similar clinical phenotypes quite frequently have very different underlying mechanisms. The tools to subdivide disease designations that are clinically identical will soon be routine. This subdivision will allow physicians to accurately diagnose a patient's disease at the molecular level and prescribe the right drug for the right patient.[10] Furthermore, a patient's overall response to a drug depends on factors that vary according to the genes that an individual carries. These factors include drug absorption, distribution, metabolism, elimination, and toxicology. These factors, too, will be easily identified in the clinical setting. With this genetic profile in hand, the physician can better select which drug to use and how aggressively to treat the individual patient.

The understanding that is gained from examining potential therapeutics at this molecular level also will lead to the development of better future therapies by incorporating this molecular information early in the drug development process.

A key component of work in personalized medicine involves

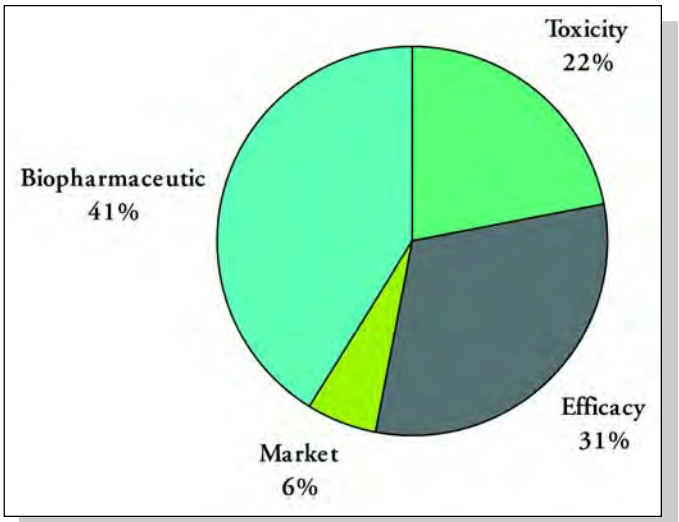

Figure 5. Why compounds fail in development.

the identification and use of Single Nucleotide Polymorphisms (SNPs). SNPs are variations in an individual's genes defined by single DNA base changes which give us our individuality. Because of their abundance in the genome (approximately one every 500 DNA basepairs) they will be used in the future to follow the inheritance of diseases, drug responses, and other traits of interest. SNP discovery is primarily a function of comparing sequences from several different individuals and identifying common sites where DNA differs. Initially, most SNPs are being discovered through high throughput sequencing; however, as the volume of sequence information continues to grow, most SNPs will be discovered through informatic analysis of existing sequence databases in the future. SNP detection in large clinical trials requires high throughput genotyping technology and informatics to track, correlate, and analyze data generated from thousands of SNPs across hundreds to thousands of patients.

These tools allow one to follow SNPs in specific genes in all individuals in a clinical trial. Associations between specific gene SNPs and drug safety, toxicity, and efficacy will be determined. This will allow for more efficient and cheaper clinical trials and for long-term benefit to the patient by being able to prescribe the right drug for the right patient as described above.

So what can we expect to see in the immediate future? Knowledge of an individual's genome, including all their SNPs will allow physicians to assess probable reactions to drugs or other therapies that might be used to treat diseases. Physicians also will be able to identify diseases for which you are at risk as well as the magnitude of that risk. Tools will become available to assess what preventive life style changes or drug therapies are important for individuals. This will truly be personalized medicine.

Conclusion

The information obtained from the sequencing of the human genome is affording the pharmaceutical industry a huge opportunity. However, the industry faces enormous challenges due to lack of productivity. To take maximal advantage of these opportunities, the drug discovery and development process must be redefined by increasing the probability of success,

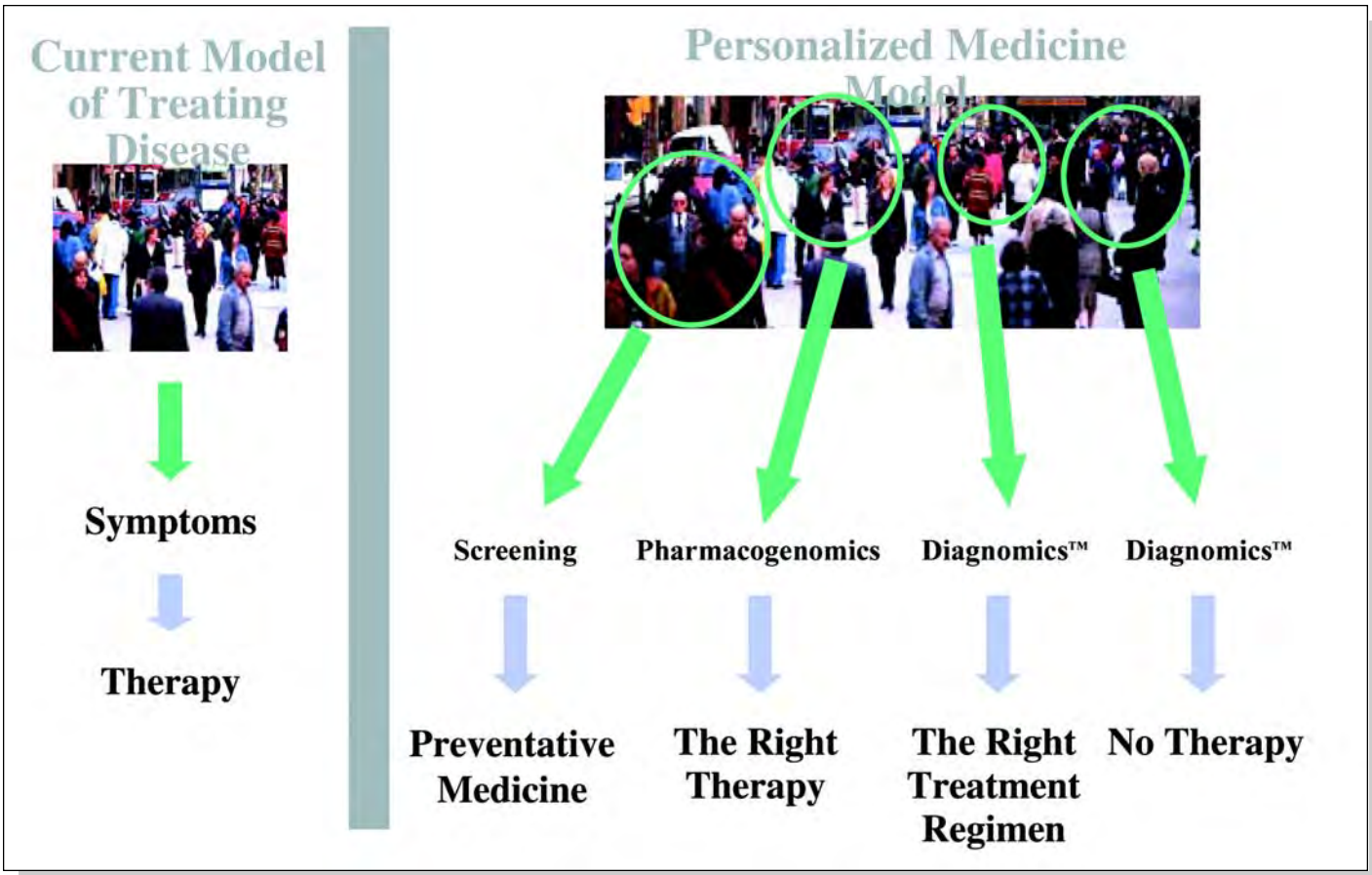

Figure 6. Personalizing medicine.

reducing the time to market, and introducing truly personalized medicine. These approaches will fuel future innovation and ultimately change the current practice of medicine.

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This article describes the history of the electrical utility industry deregulation and the changes that have taken place within the industry that directly relate to pharmaceutical facilities. It discusses changes in the National Electrical Code that will affect the reliability of the electrical distribution systems in the pharmaceutical facility.

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Economic and Reliable Power Sources for Pharmaceutical Facilities

by Joseph F. Maida, PE

Introduction

Understanding how electricity gets from its point of origin to its point of use along with the history of the regulation and deregulation of the electrical utility industry will aid pharmaceutical companies in evaluating how to purchase and distribute electricity in their facilities. Because of governmental deregulation on the national and state level, electrical power, which was once taken for granted, is now being bought and sold like a commodity. With this, new codes adopted as law by every local governmental body in the country continue to change how electricity can be distributed within pharmaceutical facilities. Understanding the power sources that exist within pharmaceutical facilities and the laws that affect these sources will assist pharmaceutical companies as they expand their electrical distribution systems and as they prepare for less reliable utility electrical power in the future. This article will begin by looking at the history of the electric utility industry and its evolution from a deregulated, to a regulated, and back to a deregulated industry over the last 100 years.

History of Deregulation in the 1980s

Pharmaceutical facilities will need more economical and reliable electrical power as the industry continues to grow. This need will only increase as people live longer, thanks in part to the development of new and better drugs by the pharmaceutical industry. What was, only 20 years ago, a much smaller industry, today the pharmaceutical industry is one of, if not, the largest industry in certain areas of the US. In southeastern Pennsylvania, the pharmaceutical industry has replaced older industries, such as steel and manufacturing, that have left the area in part due to the high cost of electricity.

When President Carter signed the Public Utility Regulatory Policies Act (PURPA) of 1978, the pharmaceutical industry's demand for electricity was small compared to the demand for electricity from older industries. As these older industries left southeastern Pennsylvania, the pharmaceutical industry was able to expand and reap the benefits these industries left behind. These benefits included a highly educated work force, many of the best universities in the country, and a political atmosphere that wanted to deregulate industries with the goal of lowering prices.

In addition to lower prices, President Carter wanted a cleaner environment. He believed that the deregulation of a number of industries would help our nation achieve both of these objectives.[1] During his four years in office, President Carter deregulated the airline and natural gas industries and laid the groundwork for the deregulation of the electrical utility and telecommunications industries. His policies led to lower prices for electricty and the development of technologies for cleaner sources of electricity. However, with deregulation, incentives, which existed within a regulated industry and caused the utility companies to invest in new power plants, would be lost. As a result, utility sources of electricity are and will continue to become less reliable.

PURPA required utility companies to purchase power from "qualifying facilities" that produced electricity as a by-product of other activities.[2] Qualifying facilities included large industrial plants that built co-generation systems. A co-generation system has a steam or gas turbine that is connected to a generator that produces electricity. The waste steam from the steam turbine or the heat generated by the gas turbine is used for processes within the facility or for heating the facility. Because of the efficient use of the fuel, co-generation systems are better for the environment than utility power generating systems that do not use their waste hest. By using the waste hest, the cost of producing electrical power by these qualifying facilities was less than the cost of their buying electricity from the electrical utility company. Some of the qualifying facilities burn waste

material from the facility's process or even trash, adding to their efficiency. Also, when the qualifying facility generated more electricity than it could use, the electrical utility was required to buy back this excess electricity. Sometimes, this was at a price higher than the price the utility could buy electricity for from other utility companies.

PURPA changed the generation, transmission, and distribution of electricity in this country, maybe forever. During the Progressive Era from 1896 to the start of World War I, utility companies were formed as a result of the government trying to regulate the generation, transmission, and distribution of electricity. Prior to the progressive era, small generating plants were built in urban areas of the country to serve residents and businesses in the local area. The government wanted the power companies to expand their distribution to larger and more rural areas. The invention of the transformer in 1885 made this possible. Transformers raise the voltage of the generated electricity to levels that will conduct large amounts of power at lower currents, thus permitting the use of smaller wires, referred to as high voltage transmission lines. Because of governments' interventions, the utility industry evolved into a monopoly that included a limited number of regulated companies. As a regulated monopoly, utility companies did not lose money on projects that had negative returns. Utility companies owned all parts of the electrical utility industry including the generation, transmission, and distribution. Their prices for electricity, although monitored by public utility commissions, could be raised high enough to always exceed their costs and essentially guarantee them a profit. New developments and innovations were shared by the utility companies through organizations like the Electric Power Research Group that was formed in 1972.

The 1980s saw the birth of high technology industries that emerged as a result of the invention of the personal computer in 1978. Together, the pharmaceutical and high technology industries are the foundation for the industrial expansion in this country today. They are also the targets for future government regulations. Without the government telling these industries where and how to expand their businesses, the pharmaceutical and high technology industries have expanded tremendously and are directly or indirectly responsible for much of the continuing demand for more reliable and economical electrical power. These expansions were not envisioned in 1978 when many politicians believed that the demand for electricity would decrease as new technological advances were developed, thus driving down the price of electricity.

History of Deregulation in the 1990s

Technical innovations and changes in governmental policies of the 1990s resulted in the development of alternative sources of electrical power and the restructuring of the electrical utility industry in many states. Gas turbine technology was enhanced because of the lower cost of natural gas, a result of the deregulation of the natural gas industry. Gas turbines were connected to generators to produce electricity as part of a cogeneration system or to run for short periods of time to satisfy daily peak electrical loads, a process referred to as peak shaving. Electric bills for pharmaceutical facilities typically include a usage charge and a demand charge. The usage charge is determined by multiplying the actual kilowatt-hours consumed by the price per kilowatt-hour. A kilowatt-hour is equal to the average amount of real electrical power, measured in watts, times 1000, times the period of time during which the

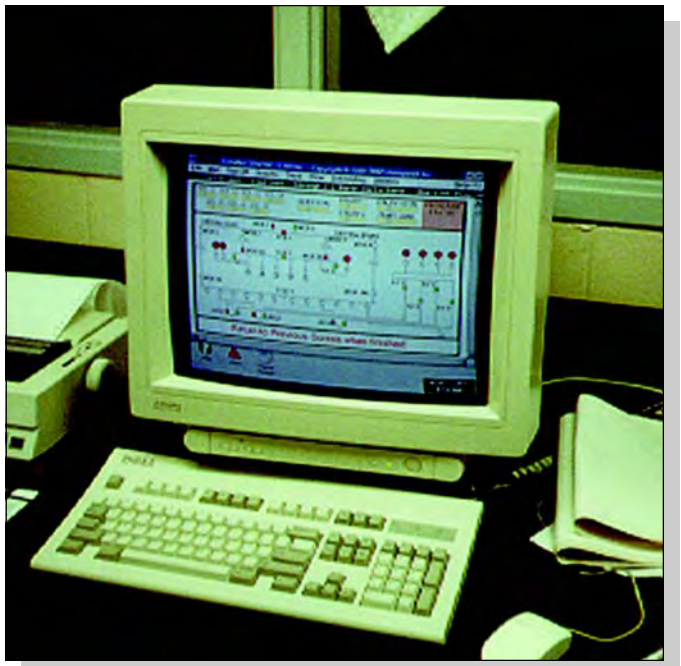

Figure 1. One of many building management system screens used to operate and monitor a 10.6 MW on-site power generating system in a pharmaceutical research facility for electrical curtailment.

average is measured. The demand charge is an additional charge added to all electrical invoices for a period (typically one year) based on the highest average kilowatt demand over a defined period of time, typically 15 minutes, which occurs anytime during the period. Therefore, a facility that has a peak electrical demand in the summer for air conditioning will pay a demand charge based on that peak demand for the next twelve months. Installation of a peak shaving generator set enables a facility to avoid excessive demand charges.

Other alternative methods for generating and saving electrical power were enhanced and explored as viable options to using fossil or nuclear fuel to generate electricity. These included windmills, geothermal, hydroelectric, and solar cells. In addition, as an alternative source for generating electricity, absorption chillers that use steam versus electricity to create chilled water for air conditioning systems, and ice storage systems that would create ice during the night and use it during the day for cooling, are forms of peak shaving. These innovations and the passage of the Energy Policy Act of 1992 under President Bush, got the attention of the electrical utility industry. Reacting to these, utility companies began to develop new rate schedules to reduce the electrical bills for their large industrial companies.

The Energy Policy Act of 1992 permitted utility companies to sell electricity anywhere in the country using transmission lines owned by other utility companies, a process that became referred to as "wheeling." Fearing that their customers would purchase power from other utility companies, the utility companies created the electrical curtailment rider. PECO, an electrical utility company in southeastern Pennsylvania, provided an incentive that reduced electrical bills for customers with a demand above 10,000 KW by as much as 50% if the customer reduced its maximum power demand to 25KW or less with 30 minutes notice. Many large facilities took advantage of this rider. Some companies could suspend manufacturing and send their personnel home and still save money because of the

savings afforded to them by the new curtailment rates. Pharmaceutical plants and research facilities could not suspend their research or manufacturing and found other ways to meet this requirement. They installed new on-site generator sets that could carry their load during the 10 to 12 hour period they were required to use less than 25 KW of utility power. Doing this, one pharmaceutical research facility in southeastern Pennsylvania saved $14,000,000 on their electrical bills over a five-year period. Their investment of $3,000,000 that added diesel engine generator sets and controls to their on-site emergency power diesel engine generators also increased their on-site emergency and standby power generating capacity to 10.6 MW. This proved to be a valuable resource even after their initial curtailment contract ended. New power companies wanted their business and possibly their on-site generating capacity as a result of deregulation.

Deregulation Today

As the 1990s came to a close, 23 states and the District of Columbia, led by California on April 1, 1998, took the next step in the deregulation of the electrical utility industry. They did this by restructuring the electrical utility industry in their state. Restructuring enabled electrical power companies, other than the local utility company, to sell electricity in the retail, consumer market. The local utility company would no longer control, and in some cases no longer own the electrical generation in their distribution area. In California, utility companies were forced to sell their generating plants. Utility companies continue to own the transmission and distribution lines and equipment in their area. Now the consumer could choose to buy electrical power from the power company that offers the lowest price and to pay the utility company for the use of their transmission and distribution lines.

Twenty of the remaining 27 states are in the process of investigating or enacting restructuring laws.[3] The seven states that have not enacted restructuring laws already have low rates for electricity. Deregulation also has affected these states by reducing their competitive edge over states that otherwise would have higher rates than they have now. Also, as would be demonstrated in June 1998, the price of electricity would increase for all states when the demand exceeds the supply. **Many electrical utility companies and other newly formed power companies have become brokers that buy and sell electricity like a commodity.** Will the supply and demand of electricity affect the availability of economical reliable electricity in the future? Now that utility companies have less incentive to build new plants, will new power companies or technologies be able to fill the demand for new electricity?

Pharmaceutical facilities, most of which are in states that have passed restructuring legislation and have high prices for electricity, can now choose the power company from whom they want to buy electrical power. Buying electricity from a power company other than the local electrical utility has reduced and may continue to reduce the cost of electrical power for large users of electrical power. In some cases, as mentioned above, power companies will provide special rate structures to facilities that have on-site generators and are willing to and capable of selling electricity back to the power company. The complexity of requiring two companies, the power generating company and the local utility company, to obtain electricity has decreased and will continue to decrease the reliability of electrical power sources in our nation. The electric power distribution system within the pharmaceutical facility also has become more complex. It too will become less reliable if it is not maintained and expanded properly as a facility's demand for electricity increases.

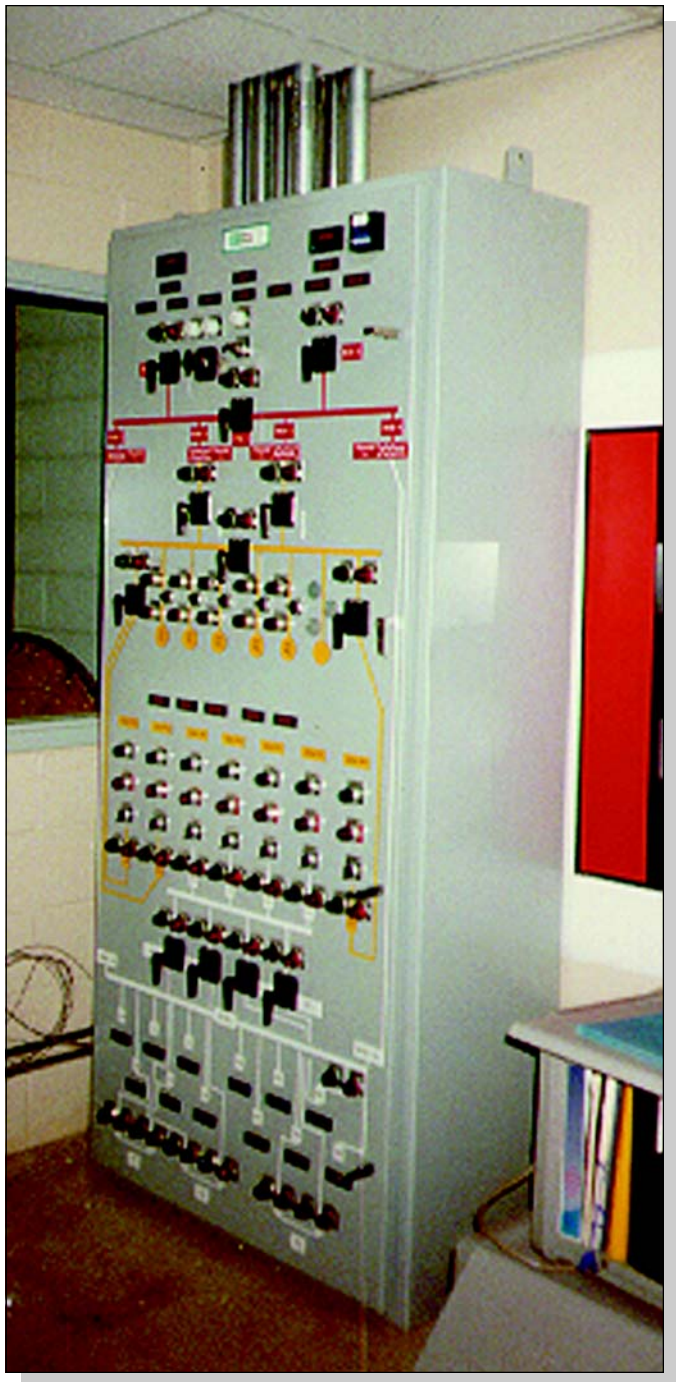

Figure 2. Circuit breaker switches, generator control switches and pushbuttons, indicator lamps, and meters used to manually parallel seven on-site generators to a utility line, to transfer load to and from the utility line, and to monitor generator and utility line loads.

New Codes and Regulations

In the interest of safeguarding the public, local governments regulate how electricity is distributed within the pharmaceutical facility. They do this by adopting the National Electrical Code (NEC) as the minimum requirement for the installation

of electrical distribution systems within buildings and facilities within their jurisdictions. When a new version of the NEC is issued, the local authority having jurisdiction usually adopts it within a short period of time. The National Fire Protection Association publishes the NEC every three years. The NEC covers everything from the installation of the primary high voltage service cables and equipment for the facility to the installation of low voltage instrumentation and control circuits.

Each new version of the NEC contains many changes and additions. New electrical installations for new construction or remodels within existing facilities must comply with the latest version of the code. Therefore, if a pharmaceutical company remodels a section of their facility, the electrical power distribution system in the remodeled section and the power distribution system that provides power to that portion of the facility must be upgraded to comply with the latest code requirements. The cost for doing this could be significant, especially for facilities that use on-site generators with non-dedicated automatic transfer switches for their egress lighting and exit signs.

Power Sources in Pharmaceutical Facilities

Changes in the 1996 and 1999 NEC include new requirements for legally required emergency power distribution systems, fire pumps, low voltage instrumentation control circuits, as well as many other items that will not be addressed by this article. To comply with the new requirements, costly changes to facilities' existing electrical power distribution system may be necessary when building an addition or remodeling an area. To understand some of the new requirements, it is necessary to be knowledgeable of the following sources of electrical power that can be found in a pharmaceutical facility.

- **Normal Utility Power** - Electricity obtained through the facility's main service entrance equipment that connects the facility to the utility's normal power line.

- **Reserve Utility Power** - Electricity obtained through the facility's main service entrance equipment that connects the facility to the utility's alternate power line. Sometimes both the normal and alternate power lines supply power to the facility at the same time in a Dual Service arrangement. These types of services are normally restricted to high voltage services. High voltage service entrance equipment usually has automatic circuit breakers and control relays that will transfer the facility load to an energized utility power line upon the loss of power on the other utility line.

- **Legally Required Emergency Power** - Electricity that serves legally required emergency loads and must be present within 10 seconds upon loss of normal utility power. Legally required emergency loads are defined within building codes and usually include emergency egress lighting and exit signs. The electricity can be obtained from a separate utility power line or can be generated on-site using emergency generator sets or batteries. Emergency generator sets must have on-site fuel sources, dedicated Automatic Transfer Switches (ATS), and dedicated power distribution equipment and circuits. Variances for use of natural gas may be obtained from the authority having jurisdiction.

- **Legally Required Standby Power** - Electricity that serves legally required standby loads and must be present within 60 seconds upon loss of normal utility power. Legally required standby loads are defined within building codes and include "heating and refrigeration systems, communications systems, ventilation and smoke removal systems, sewerage disposal, lighting systems, and industrial processes, that, when stopped during any interruption of the normal electrical supply, could create hazards or hamper rescue or fire-fighting."[4] The electricity can be obtained from a separate utility power line or can be generated on-site using emergency generator sets or batteries. Standby generator sets require on-site fuel sources but do not require dedicated Automatic Transfer Switches (ATS) and dedicated power distribution equipment and circuits.

- **Optional Standby Power** - Similar to Legally Required Standby Power, except that the loads are selected by the facility and include critical systems and equipment within the facility.

Small pharmaceutical plants as well as administrative offices may not have a reserve utility power source, a legally required standby power source or an optional standby power source. Facilities that decide to install an additional ATS to comply with the new NEC requirements may need to replace their existing ATS as well. Whenever more than one ATS is installed on a power distribution system, it is sometimes necessary to switch the neutral conductor in addition to the three phase conductors.[5]

Reliability of Power within the Pharmaceutical Facility

The reliability of normal and reserve (alternate) utility power lines in most major metropolitan areas has been very high. Concurrent power failures on both utility power lines could have happened once every five years before restructuring. In the future, with the utility companies having fewer incentives to increase existing or continue to own power generating capacity, power failures of both sources might occur more often. **On-site optional standby power generating systems will become an increasingly essential part of a pharmaceutical facility's infrastructure.**

Many pharmaceutical facilities built prior to 1996, installed on-site power generating capacity for all or a significant portion of the load within their entire facilities. Others added additional electrical power generating capacity to enable them to take advantage of electrical power price incentives offered by the public utilities. Common automatic transfer switches were installed to transfer power from the public utility to the on-site diesel or gas powered generator sets upon loss of utility power. The 1996 NEC requirement for dedicated automatic transfer switches for new legally required emergency loads, in many cases, makes the use of the existing emergency generators unfeasible for legally required emergency loads. New generators or other sources of legally required emergency power are required.

Generally, emergency egress lighting fixtures and exit signs with internal batteries (unit equipment) or centrally located storage batteries or uninterruptible power supplies can be used in lieu of on-site generators to satisfy building code and NEC requirements for legally required emergency systems. Unit equipment is very reliable, but has a high maintenance cost. Unit equipment is typically designed to operate for 1.5 hours, the minimum time allowed by the NEC. Unit

equipment has an advantage over other types of emergency power equipment because unit equipment will detect the loss of power at point of use and provide almost immediate illumination to the affected area. An area can lose power because of a failure to the electrical circuit feeding the area. This is one reason why the NEC requires that all electrical circuits, and now even the ATS that serve legally required emergency loads, be dedicated and separated from the normal power distribution circuits.

On-Site Generators

Generators are available in many sizes and voltages and with engines that can run on one or even two types of fuel. For both legally required emergency and standby loads, generator sets that use internal combustion engines as their prime mover must be provided with an on-premise fuel supply sufficient for not less than two hours of operation at full load. Sizing a generator for a specific building or specific loads is fairly simple. Computer programs are available to aid in this effort. As the number of on-site generators increases within a facility, the amount of excess or contingent power that could be used if it could be distributed to other parts of the facility becomes a consideration. Also, as a facility grows or changes, the location of local generators or the space available to install new local generators often presents a problem. The installation of central generator sets with priority load shedding can eliminate this problem. This approach also will reduce the amount of unusable excess or contingent generator capacity that is installed within the facility. The generator sets, if not intended to operate for weeks at a time,[6] can have standby rated engines versus prime rated engines. They also can be loaded to their full nameplate capacity. Generators that are intended to be the prime source of power, or intended to operate in parallel with the normal utility power source continuously, should be prime rated.

A major disadvantage of having only a central power generating system is that the system cannot provide power to selective loads that lose power due to a failure in the facility's power distribution system. This potential problem can be greatly reduced by installing a redundant power distribution system. Problems within the system that occur at the local levels require much less time to repair than a problem within the main facility power distribution system (e.g. the replacement of a main distribution transformer versus a local lighting transformer). Another way to prepare for a local failure is to make provisions for the temporary connection of a portable generator that usually can be rented quickly. A portable generator can be used for non-legally required standby loads. It also can be used as the backup to the normal emergency generator. The normal emergency generator must have a backup when it is out of service for more than a few hours for maintenance.[7]

Large pharmaceutical facilities should consider having two utility power sources, redundant primary voltage feeders and transformers, and a combination of centrally located, primary voltage emergency generators with some smaller, utilization voltage, local emergency generation for legally required emergency loads and some legally required and critical standby emergency loads. Smaller pharmaceutical facilities also should consider having two utility power sources, one at a primary voltage level (above 12KV), and one at a utilization voltage level (480V or 208V) with a central emergency generator at utilization voltage that can be used for emergency and standby loads. In many cases, the power companies will not provide the primary service because the facility load is below their requirements for this type of service.

Each pharmaceutical facility must evaluate their requirements with the cooperation of the local utility company. Before a utility company will permit a facility to connect their on-site generators in parallel with the utility's supply line, protective relaying and sometimes grounding transformers will need to be installed. The engineering and design for systems that operate in parallel can be quite significant, but is necessary to safeguard other utility customers that may be connected to the same supply line as the pharmaceutical facility.

Automatic selective load pickup and load shedding is needed to ensure adequate power to (1) the emergency circuits, (2) the legally required standby circuits, and (3) the optional standby circuits, in that order of priority. Electrically operated circuit breakers controlled by a programmable logic controller or a reliable building management system combined with two or more generator sets provides a reliable source of emergency power.

Fire Pumps

When designing a new power distribution system or adding a new building that requires an electric fire pump, the requirements for providing both normal and emergency power to the fire pump must be considered. The NEC does not require that a fire pump be on emergency power if the electric utility service is reliable. Public utility companies have however, mandated that their power line not be the only source of electric power to a fire pump. In most cases, fire pumps would be a part of the facility's legally required emergency load. Because the fire pump will normally be rated at utilization voltage (480 Volts) and not primary voltage and because it requires a separate service or must be connected ahead of the main service entrance equipment, the provision of a second, utilization voltage service has some advantage. It eliminates the cost for a dedicated transformer when a primary service is installed.

Consideration for Future Expansion:

Many pharmaceutical facilities will need to modify their existing normal and emergency power systems to

Figure 3. 1,600 Kilowatt and a 1,400 Kilowatt (background) - 13,200 Volt, 3 phase diesel engine emergency generator set.

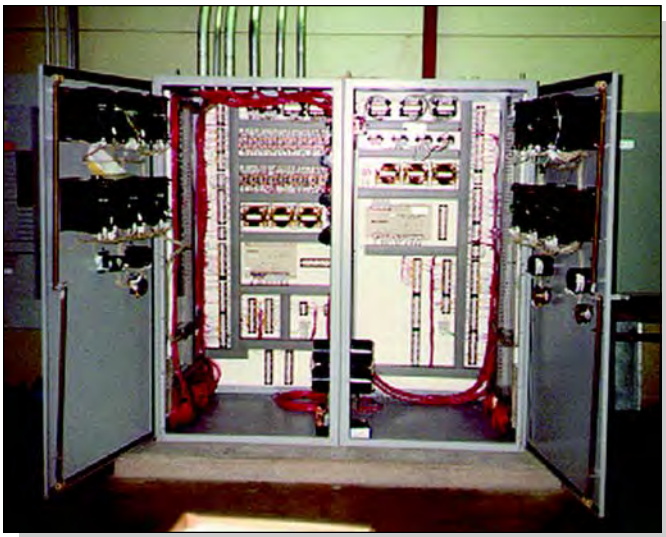

Figure 4. Protective relays, control relays, synchronization controller and load transfer controllers used to parallel a pharmaceutical facility's generators with the utility supply line.

meet future power demands. Decisions relative to future requirements for emergency power will depend on the type of facility (research, manufacturing, or administrative). It also will depend on the financial impact that could result from the loss of power (e.g. the loss of a research project) and on management's philosophy. These decisions have always been complex and are now even more intricate. A thorough understanding of the present and future normal and emergency power system and the complexities of how the power systems can be expanded in the future will enable the plant engineer to increase the reliability of the facility's power system. It also will create an overall awareness of the significant hidden cost that should be part of any analysis of the facility's future capital expenditure plans.

Instrument and Control Power Supplies

When evaluating new designs and installations, the pharmaceutical industry should not forget their low voltage instrumentation and control systems and the NEC requirements for their power supplies. The requirements for these also have changed with the adoption of the 1996 NEC. Prior to 1996 NEC, a 12 Volt DC power supply rated above 100 watts could be used for instrumentation and control systems that had cables and wires rated below 600 volts and in sizes smaller than #18 gauge as long as the wires were fused. Since the 1996 NEC, the 12 volt power supply for this type of cable or wire must be UL Listed or Labeled as a Class 2 power supply, whether the wires are fused or not.[8] What seems to make perfect sense, using a 300 volt cable for a 12 volt circuit, may now violate the NEC because this type of cable can no longer be used with the non-Class 2 power supply that was commonly installed on most instrument and control circuits prior to 1996.

Be Aware

Pharmaceutical facility managers and plant engineers must be aware of new requirements within codes as they expand and add new loads to their facilities. They also should be aware of opportunities to obtain alternate sources of economic and reliable electricity. The present and future cost of reliable electrical power should be a part of any pharmaceutical facility's Strategic Corporate Plan. Knowing what happened to other industries, partly because of the loss of their competitive edge due to the high cost of electricity, may assist the pharmaceutical industry in finding new reliable sources of economical and reliable electricity. **Knowing what happened a few years ago should strike more fear into the pharmaceutical industry's risk managers than Y2K did last year.**

Answer to Questions

Imagine what would happen if a residential customer received a $5,000 electric bill. This might have happened in June 1998 had areas of the Midwest been deregulated. On June 25, 1998, the wholesale price for electricity in the Midwest went from average prices of $25 to $40 per megawatt-hour (1,000 kilowatt-hours) to a peak price of $7,500 per megawatt hour. Reportedly, Commonwealth Edison (Chicago) paid $4,000,000 for $100,000 worth of electricity.[9] Also on that day, at 11:00 AM, the Pennsylvania New Jersey Maryland Interconnect (PJM), which incorporates all transmission lines in southeastern Pennsylvania, declared a "maximum emergency" and discontinued selling electricity to the Midwest. At the same time they curtailed many of their large customers. These customers included a number of major pharmaceutical facilities. PJM was permitted to cut off power transactions with the Midwest because of destabilizing power flows in their system. This cut-off was in accordance with a recent ruling from the North American Electric Reliability Council (NERC). NERC was established in the wake of the 1965 Northeast Blackout that was caused by instability in the PJM system. Also, as a result of the June 1998 price surge, some newly formed power companies went out of business. Knowledge of the past prepares one for the future. To read more about this and other aspects of deregulation go to Smithsonian Institution Powering a Generation of Change Web Page at http://americanhistory.si.edu/csr/powering/.

Get Professional Help

This article was written to assist **Pharmaceutical Engineering's** readers in understanding today's power systems and their requirements. All statements contained herein are believed to be accurate, but they are not intended to replace design standards or codes. Before using the information contained herein, the reader should refer to the latest versions of applicable codes and standards, or consult with a Professional Engineer.

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2. Smithsonian Institute – Powering a Generation of Change - http://americanhistory.si.edu/csr/powering/

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9. June 30, 1998 Energy Online Daily News.

About the Author

Joseph F. Maida has a BS and an MS in electrical engineering from Drexel University. He was a licensed electrical contractor, an officer in the US Army Reserves, and an employee of two public utility companies and a consulting engineering firm prior to starting his own company in 1978. As president of Maida Engineering, Inc. for the last 22 years, he has managed a multidiscipline engineering, design/build, and systems integration firm that has worked in many large and small pharmaceutical facilities He is a registered Professional Engineer in a number of states and has consulted on, engineered, and overseen the design and construction of power, control and instrumentation systems throughout the US and overseas.

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This article summarizes survey results taken in the spring of 2000 on the use of barrier isolators in fill/finish applications in the parenteral industry.

For complete survey raw data, log on to the ISPE Web site - www.ispe.org.

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Barrier Isolation History and Trends, A Millennium Update

by Jack Lysfjord and Michael Porter

This is an update from a 1998 survey on the global trends on barrier isolation usage for automated (non-manual) fill finish operations. The survey took place during March-May 2000 and summarizes findings from vendors and users. Data was first presented in June 2000 at the ISPE Barrier Isolation Technology Conference and updated in September of 2000.

This survey showed an increase in number of units from 84 in the 1998 survey to 172 in 2000. Figure 1 shows the deliveries/year with the dotted vertical line indicating that 2001 and 2002 deliveries are planned, but data can increase for these years depending on additional orders. Over the past five years, global deliveries of barrier isolators have averaged 22/year.

Figure 2 breaks down the previous data into usage by continent. Europe has historically been the leader over North America. Growth is occurring in North America. Japan is beginning to use the technology and one unit appears in Africa.

Figure 3 indicates companies that are committed to this technology. The number of companies using the technology increased from 38 in 1998 to 56 in 2000. The number of filling lines reported in operation increased from 34 in 1998 to 70 in September 2000. FDA approval increased from 6 to 26 in the same period. The time from delivery to start of operation is shown in Figure 4. Type of container and maximum speed is shown in Figures 5 and 6.

Barrier isolator construction is continuing to be dominated by hard wall designs (stainless/glass) with 134 versus 9 soft wall units. In 1998, the numbers were 73 and 9 respectively. Surrounding room classification results are shown in Figure 7 and sterilants used are shown in Figure 8.

Systems design of open barrier isolator (continuous motion) is 83 versus closed (batch process) of 20. Figure 9 shows barrier isolator pressure to surrounding room with Figure 10 showing the pressure to the washer room for open systems.

Containment is a growing need and utilization of barrier isolation for the containment application is shown in Figure 11. Cumulative deliveries of systems for fill/finish applications are shown in Figure 12.

Several questions on glove usage were asked to support a glove discussion at the June conference. There is a preference for two piece gloves (glove and sleeve) over one-piece glove/sleeve by 51/35 ratio. Smooth sleeves were preferred over pleated (accordion or bellows) sleeves by 40/11 ratio. A second disposable glove is preferred by 70/25 ratio over no second glove and glove integrity tests are typically performed by 72 where 23 do not test. Methods of integrity testing are shown in Figure 13. Typical glove replacement periods are shown in Figure 14. Only 17 lines utilize half-suits. Preferences based on this survey indicated:

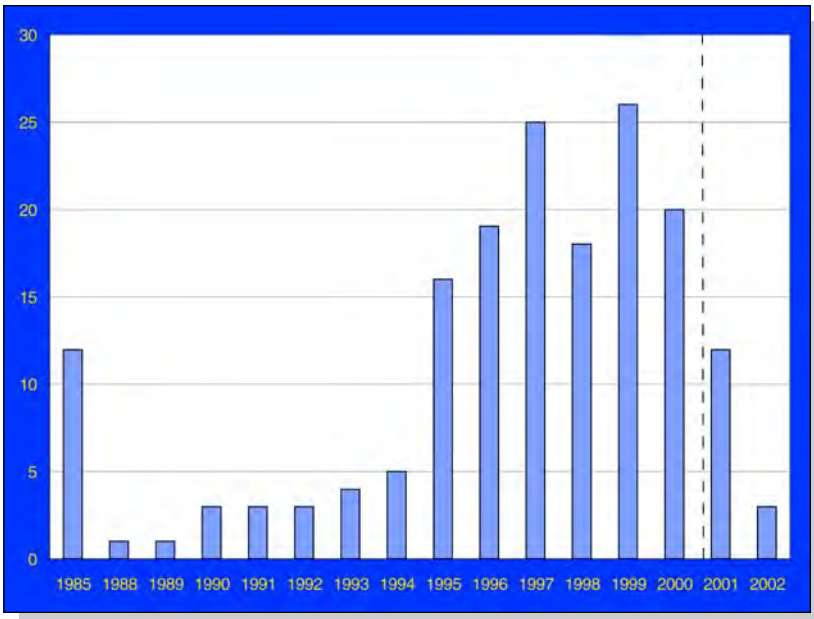

Figure 1. Barrier isolator filling line deliveries by year.

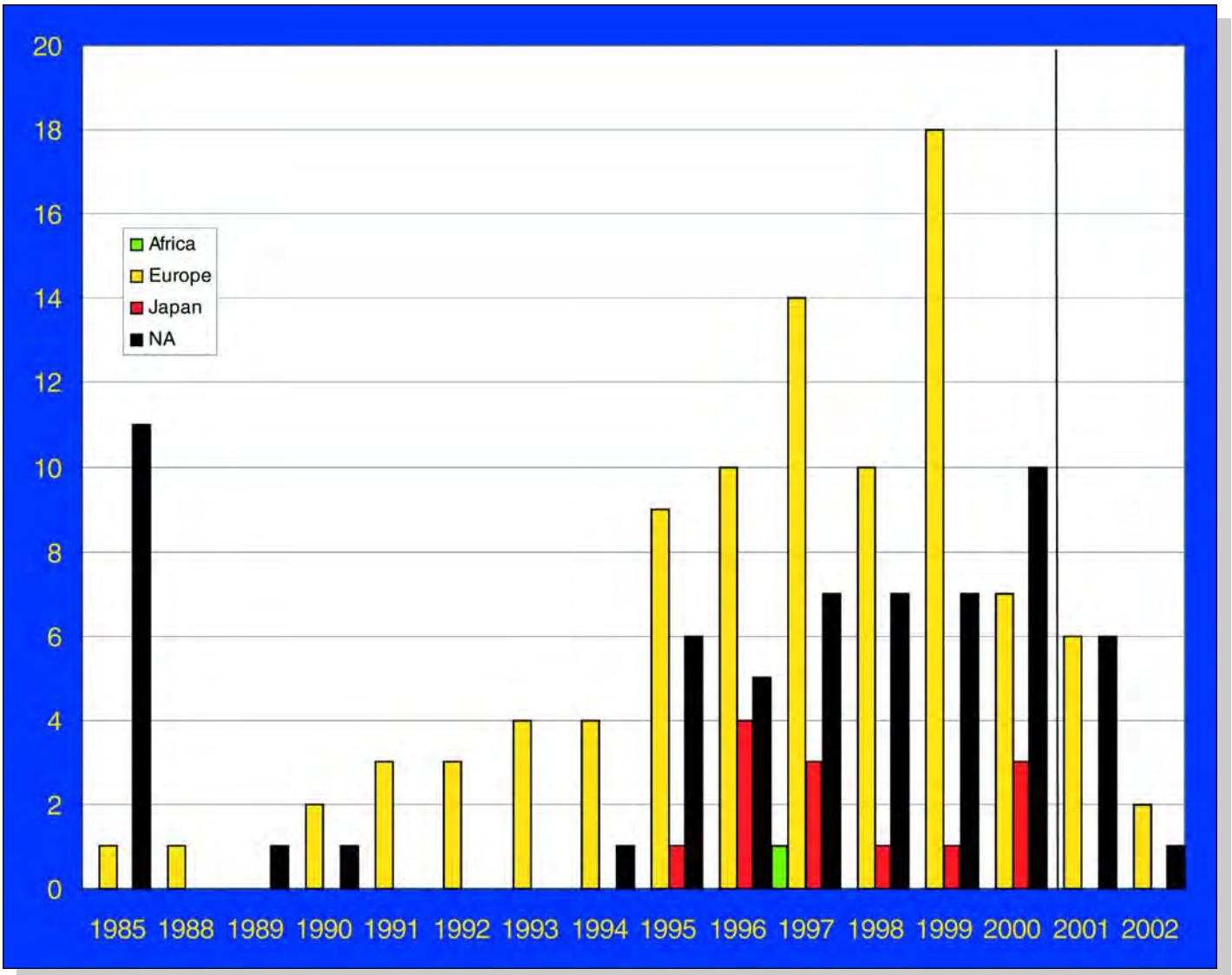

Figure 2. Barrier isolator filling line deliveries by year and region.

- Hard Wall Barrier Isolator
- Vaporized H_2O_2 Sterilant
- Class 100,000 Surrounding Room
- Minimal use of Half-Suits, Mainly Gloves
- Two Piece Gloves with Smooth Sleeves
- Use of a Second Disposable Glove
- Most perform Glove Integrity Tests

The use of barrier isolation technology has shown significant growth over the past two years and is continuing to grow. These data are presented to help show an important industry trend in parenteral fill/finish operations, a trend that should be considered by manufacturers of aseptically filled products.

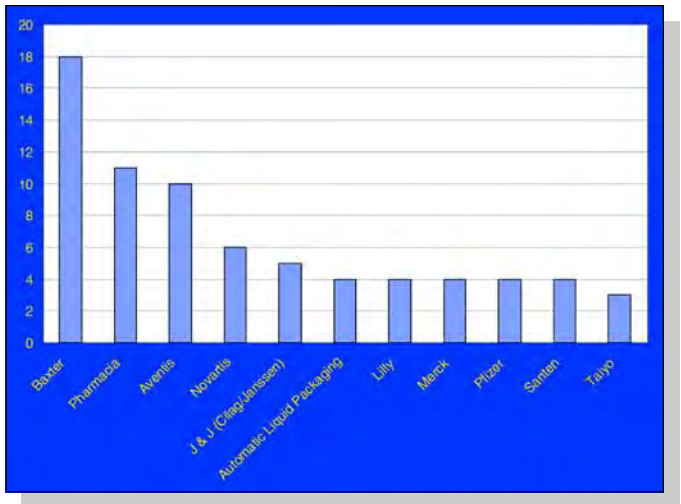

Figure 3. Barrier isolator filling lines - companies with highest usage.

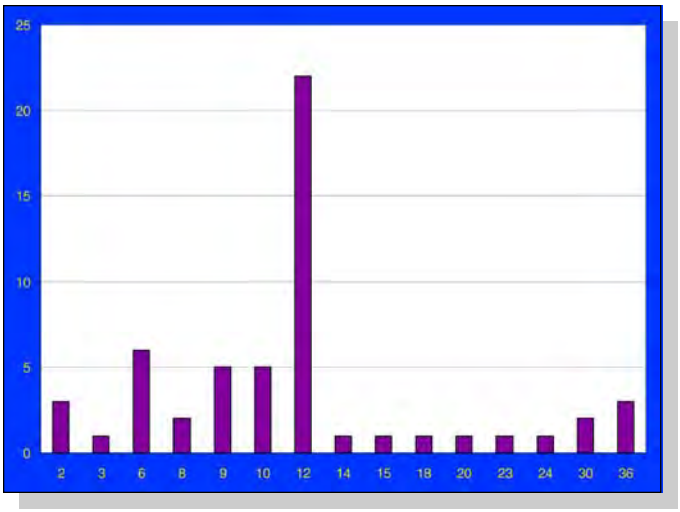

Figure 4. Months from delivery to start-up (55 responses).

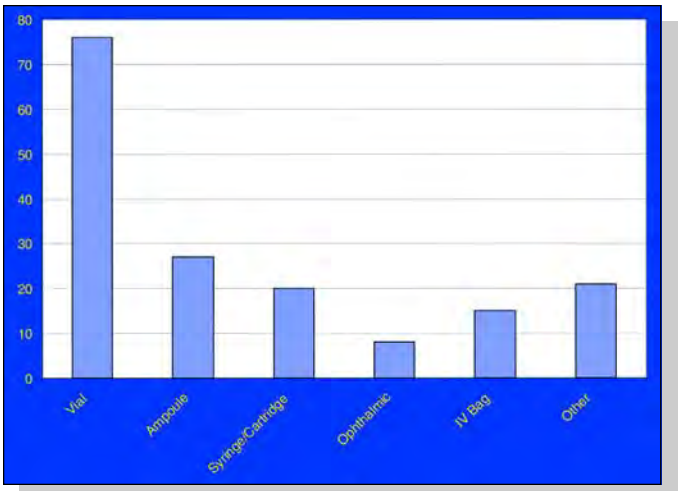

Figure 5. Type of container (167 responses).

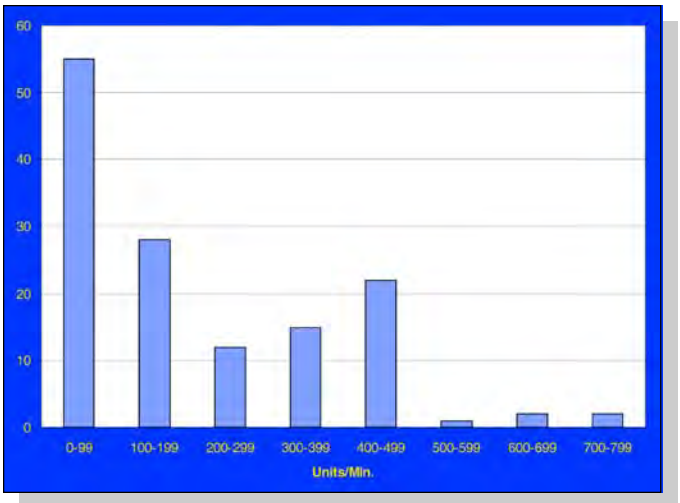

Figure 6. Maximum speed (137 responses).

	1998	2000
100	3	4
1,000	3	4
10,000	13	30
100,000	55	84
Unclassified	5	17
Response Total	79	139

Figure 7. Barrier isolator surrounding room classification.

H_2O_2 Vapor	108
H_2O_2 Spray	13
H_2O_2 + Steam	1
Miscellaneous PAA (peracetic acid)	6
Formalin	1
ClO_2	1
Alcohol Wipe	2
Other	5
Total	137

Figure 8. Barrier isolator sterilants.

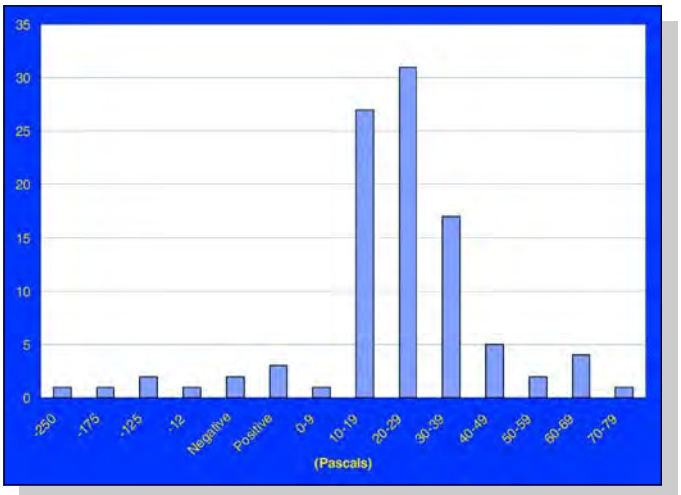

Figure 9. Pressure to surrounding room - Pascals (98 responses).

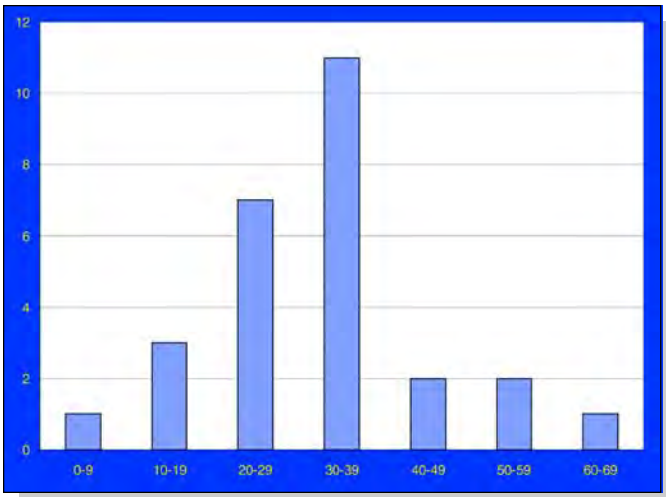

Figure 10. Pressure to washer room - Pascals (27 responses).

Yes			17
	Chemical	**12**	
	Biological	**2**	
	Chemical Biological	**1**	
	Chemical Nuclear	**2**	
No			76
Total			93

Figure 11. Barrier isolators indicating need for containment.

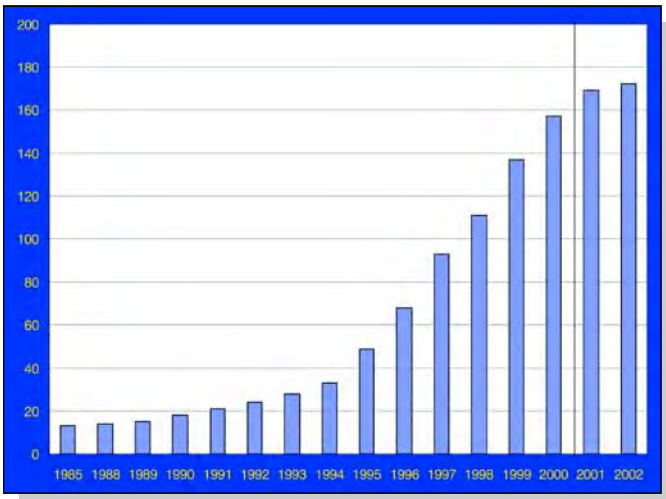

Figure 12. Barrier isolator filling line - cumulative deliveries (172 total).

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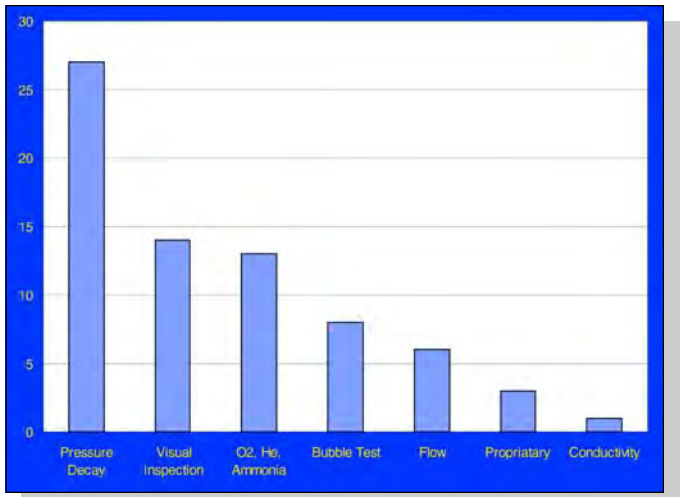

Figure 13. Method for integrity testing of gloves (72 responses).

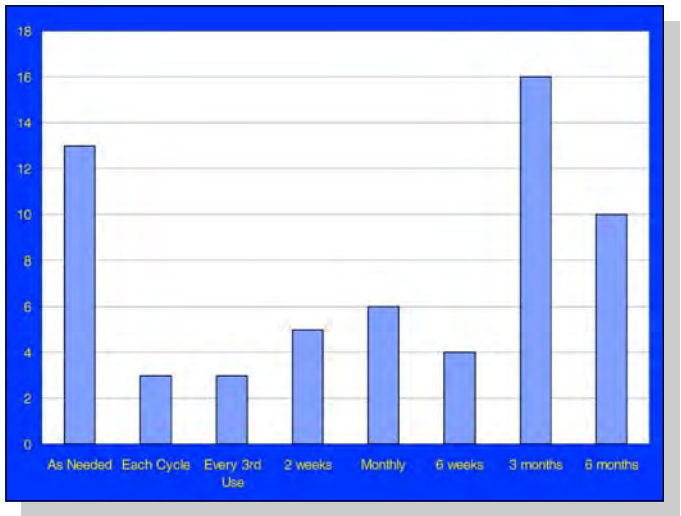

Figure 14. Glove replacement period (60 responses).

(BUGS). He is a frequent speaker and course leader in the US, Europe, and Asia, and has been author and co-author for numerous technical papers and articles. He has served as chairman of ISPE's annual Barrier Technology Conferences in the US and Europe. Lysfjord holds a BS in mechanical/industrial engineering from the University of Minnesota and a MBA from the University of St. Thomas.

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This article provides a brief Executive Summary of the Commissioning and Qualification Baseline® Guide.

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Baseline® Guides Update

Introduction

The first goal of the Commissioning and Qualification Guide is to bring a common terminology and methodology to the commissioning and qualification process that can be used by manufacturers, facility designers, contractors, and equipment suppliers.

The Commissioning and Qualification Guide defines systems in terms of their function and consequent impact on product quality, which determines the level of commissioning and qualification required.

- **"Direct Impact" systems** are expected to have an impact on product quality
- **"Indirect Impact" systems** are *not* expected to have an impact on product quality

Both types of systems will require **commissioning.** However, the "Direct Impact" systems will be subject to supplementary **qualification practices** to meet the additional regulatory requirements of the FDA and other regulatory authorities.

The second goal of this Guide is to provide a System Impact Assessment process to bring structure and consistency to determining whether a system is a "Direct Impact" system or "Indirect Impact" system.

This differentiation between system type will determine the attention and effort given to each and by whom. Therefore, the determination as to whether the system is "Direct" or "Indirect" impact is critical. **System Impact Assessment** provides both the thought process and some key questions that must be asked in making the determination.

System Impact Assessment is an informed judgment, made by a group of appropriately qualified stakeholders and should be based on a comprehensive understanding of the product, process, and the nature of the systems and components. This decision should be justified and made explicit, in a concise manner, through the production of a QA-endorsed **Impact Assessment Rationale** for each system.

The **Impact Assessment Rationale** for each system should also document the component criticality assessment in a similar manner.

An interdisciplinary team approach to commissioning and qualification will help establish an effective basis for master planning and execution of facility projects. Specifically, the Guide is focused upon value added approaches that will eliminate duplication of effort and the costly practices of:

- repeating qualification steps during process validation
- qualifying systems that only require commissioning
- generating insufficient or excessive documentation

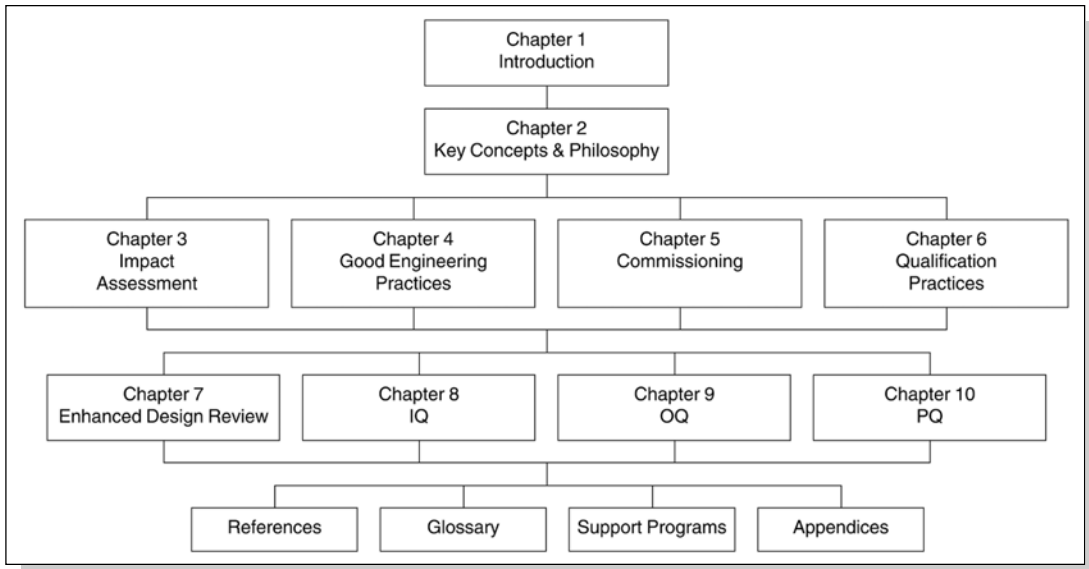

Figure 1. Chapter structure.

- Excessively long project schedules
- Delays which can result in product supply interruptions or delayed product launches

Guide Philosophy and Key Concepts

This Chapter describes the purpose and philosophy of the Commissioning and Qualification Guide, and the differences between the commissioning and qualification processes in the context of this Guide. It is important to understand and apply the approaches outlined in this Guide in a sound and well-reasoned manner, since every facility and project is different. The key terms used in the Guide are defined, including:

- "Direct Impact" System
- "Indirect Impact" System
- "No Impact" System
- Design for Impact
- Good Engineering Practice
- Enhanced Design Review
- Commissioning

An overview of Qualification Practices is given, including Enhanced Design Review, Installation Qualification, Operational Qualification, and Performance Qualification. V-models are provided for both "Direct Impact" systems and "Indirect Impact" systems and the role of Quality Assurance is discussed.

Impact Assessment

Impact Assessment is the process of determining which systems and/or system components should be subject to Qualification Practices in addition to Good Engineering Practices (GEP). Impact Assessment assists in defining the Commissioning and Qualification scope of a project.

This Chapter considers the Impact Assessment process. Terms specific to Impact Assessment are defined. A method is suggested for defining the steps of a system assessment process, including a discussion of the benefits, and a list of the criteria for determining system impact and component criticality.

Good Engineering Practice

This Chapter provides an overview of the various project phases and sequence, from inception through commissioning, qualification, and operation. Concepts associated with "Good Engineering Practice" (GEP), the types of activities that occur, and documentation that is created through GEP are discussed. Overviews are provided of both effective project controls, and project team concepts and organization. The Requirements phase is considered in detail, including:

- Project Purpose and Justification
- User Requirements Brief
- Requirements Specifications
- Project Execution Plan
- Maintenance and Technical Support Requirements
- Compliance Requirements
- Deliverables

Stages in the design process are described with specific consideration of Piping and Instrumentation Diagrams, Specifications, and Construction drawings. Construction involves several elements, which are crucial to every project, including project site logistics and project quality control. This Chapter details typical requirements and elements of construction.

The information given in the Chapter aims to demonstrate how GEP, as applied throughout the project lifecycle, provides a basis for effective qualification.

Commissioning

This Chapter defines the term "commissioning" in the context of the Guide and describes the organization and content of the Commissioning Plan document. Commissioning is positioned within the context of the Qualification effort and guidance is provided in the management and execution of the commissioning activities. Typical commissioning deliverables and the associated commissioning team responsibilities are considered. Commissioning activities described include:

- Inspection
- Setting-to-Work
- Regulation and Adjustment
- Testing and Performance Testing
- Training
- Turnover
- Commissioning Plan Close-Out

Qualification Practices

"Direct Impact" systems are subject to qualification practices that incorporate the enhanced review, control, and testing against specifications and requirements necessary for compliance with current Good Manufacturing Practice. The purpose of this chapter is to introduce a high level overview of qualification practices that are required for "Direct Impact" systems. The Validation Master Plan and Qualification Rationale are described in detail. This Chapter contains detailed consideration of Enhanced Documentation.

Enhanced Design Review

Enhanced Design Review (EDR) is the term adopted by this guide to describe the process by which engineering designs for pharmaceutical facilities, systems and equipment are evaluated. This process compliments *Good Engineering Practice.*

This Chapter gives the regulatory perspective on EDR and relates EDR to the V-Model for "Direct Impact" systems. The EDR process is detailed. A structured design review method and a failure modes analysis method are suggested for evaluating designs.

Installation Qualification

Installation Qualification (IQ) is an activity that is regulated by the FDA, and is a part of final qualification activities before process validation begins. The primary objectives of this chapter are to:

- provide an overview of the Installation Qualification process
- describe the types of activities that occur and documentation that is needed for the Installation Qualification Process

- describe how Installation Qualification fits in with the overall qualification process
- describe how Commissioning integrates within the Installation Qualification process

Operational Qualification

Operational Qualification (OQ) is an activity that is regulated by the FDA, and is a part of final qualification activities before Performance Qualification or Process Validation begins. The primary objectives of this chapter are to:

- provide an overview of the Operational Qualification process
- describe the types of activities that occur and documentation that is needed for the Operational Qualification Process
- describe how Operational Qualification fits in with the overall qualification process
- describe how the commissioning process integrates within Operational Qualification

Performance Qualification

Performance Qualification (PQ) is an activity that is regulated by the FDA, and is the final qualification activity before the remainder of Process Validation begins. For pharmaceutical grade utilities and certain support systems, PQ is the final qualification step.

Once the system (or systems) have gone through IQ and OQ execution and have been approved/accepted the PQ can be performed. The primary objectives of this chapter are to:

- provide an overview of the Performance Qualification process
- describe the types of activities that occur and documentation that is needed for the Performance Qualification Process
- describe how Performance Qualification fits in with the overall qualification process
- describe how the commissioning process integrates within Performance Qualification

Related Programs

This Chapter provides details of those programs that are undertaken to provide assistance and information in support of the qualification activities. Some of these programs can be applied to 'Direct', 'Indirect' and 'No Impact' systems and their components. Where these programs are undertaken in support of qualification activities, the appropriate qualification practices must be followed to ensure that the compliance of the overall qualification effort is not compromised. Related programs considered include, Safety, Training, Preventative Maintenance and Calibration, Computer Systems Validation, and Revalidation.

Glossary

Terms and concepts used throughout the Commissioning and Qualification Guide are defined and cross-referenced.

Illustrative Examples

The illustrative examples given in this Chapter provide one interpretation of how the key concepts of this guide can be applied in preparing for commissioning and qualification activities. Depending upon company policies or the intended use of the equipment listed, there may be additions or deletions to the listed activities.

Appendix

The Appendix provides detail and references for Failures Modes Analysis. The principle of which is to consider each mode of failure of every component and to ascertain the effects on system operation in turn. The FMECA process produces a quantified measure of reliability.

Conclusion

The Commissioning and Qualification Guide is intended for use by industry for the design, construction, commissioning, and qualification of new or newly renovated manufacturing facilities that are regulated by FDA or other health authorities. The Guide provides advice and guidance that may be applied to all types of facilities, utilities, and equipment found in the healthcare industry.

The focus of this Guide is on the engineering approaches and practices involved in providing cost effective manufacturing facilities in a timely manner that meet their intended purposes.

This is Part One (A-B) of a glossary that can be viewed in its entirety on the ISPE Web site ISPE.org.

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Pharmaceutical Glossary: A-B

by Michelle M. Gonzalez

- A -

Abiogenesis - Spontaneous generation. *(also see: Biogenesis)*.

Abiotic - Absence of living organisms.

Absolute Configuration - The configuration of four different substituent groups around an asymmetric carbon atom, in relation to D- and L- glyceraldehyde.

Absolute Humidity - *(also see: Specific Humidity)*

Absolute Purity Water - Water with a specific resistance of 18.3 megohm-cm at 25°C. *(also see: Resistivity)*

Absolute Rating - The diameter of the largest hard spherical particle that will pass through a filter under specified test conditions. An indication of the largest opening in the filter element. An absolute rating may be validated by a number of nondestructive tests.

Absorption - The assimilation of molecules or other substances into the physical structure of a liquid or solid without chemical reaction.

Absorption - The removal of a specific antigen or antibody from a sample by adding the corresponding antibody or antigen.

Absorption - The transport of the products of digestion from the intestinal tract into the blood.

Acceptance Criteria (for HVAC) - The limits of conditions of room environment (critical parameters) that may affect the product's SISPQ (Strength, Identity, Safety, Purity, or Quality). These conditions may include temperature, humidity, and room air quality. For example, if humidity or airborne particles are not critical parameters affecting SISPQ they are not included in acceptance criteria. Also, an acceptance criterion may be imposed on the performance of a piece of equipment, such as HEPA filter efficiency or face velocity.

Acceptance Criteria - The acceptable limits of a GMP Critical Parameter to ensure product SISPQ (Strength, Identity, Safety, Purity, or Quality).

Acceptance Criteria - The criteria a product must meet to successfully complete a test phase or to achieve delivery requirements. This is usually associated with a performance qualification. It may require an exact result (such as the ability of a bar code system to identify correct or incorrect codes) or it may state an acceptable range (such as an incubator demonstrating the ability to maintain a temperature set point plus or minus a given tolerance).

Acceptance Criteria - Measurable terms under which a test result may be considered acceptable. (Most common definition)

Acceptor Control - The regulation of the rate of respiration by the availability of ADP (Adenosine Diophosphate) as phosphate acceptor.

Acceptor Junction Site - The junction between the right end of an intron and the left end of an exon.

Access Floor System - An assembly consisting of panels mounted on pedestals to provide an under-floor space for the installation of mechanical, electrical, communication, or similar systems or to serve as an air-supply or return-air plenum.

Accession - The addition of germplasm deposits to existing germplasm storage banks.

Accidental Release - The unintentional discharge of a microbiological agent (i.e., microorganism or virus) or eukaryotic cell due to a failure in the containment system. Accidental releases may be *de minimis* in nature. *(also see: Incidental Release)*

Acclimatization - The biological process whereby an organism adapts to a new environment. One example is the process of developing microorganisms that degrade toxic wastes in the environment.

Accommodation Schedule - Defines all areas that can influence unit operations required for manufacturing, and relationships and flows between them.

Account Policy - Specifies how passwords must be defined and employed for all user accounts on a system. It specifically addresses the issues of password aging, password uniqueness, and locking a user account because of invalid logon attempts. CFR 21 Part 11 mandates technical controls in these areas specifically.

Acid - A compound of an electronegative element or radical with hydrogen; it form salts by replacing all or part of the hydrogen with an electropositive element or radical. Or, a hydrogen-containing substance that when dissolved in water dissociates to produce one or more hydrogen ions (H+).

Acid Feed - Injection of an acid into a liquid stream to make it less alkaline (pH adjustment).

Action Limit - *(also see: Action Point)*

Action Point - A value set to identify when a parameter has drifted outside the operating range (Acceptance Criteria). A documented response is usually required.

Activated Carbon - Material used to adsorb organic impurities from water. Derived from wood, lignite, pulp-mill char, blood, etc. The source material is initially charred at high temperature to convert it to carbon. The carbon is then "activated" by oxidation from exposure to high temperature steam. It comes in granular or powdered form.

Active Immunity - The formation of an antibody that can be stimulated by infection or vaccination.

Active Ingredient - Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect. *(also see: Inactive Ingredient)*

Active Pharmaceutical Ingredient - *see: API (Active Pharmaceutical Ingredient)*

Active Site - The region of a protein molecule that binds the specific substrate and chemically modifies it into the new product (in an enzyme) or interacts with it (in a receptor).

Active Transport - Energy-requiring transport of a solution across a membrane in the direction of increasing concentration.

Actual Yield - The quantity that is actually produced at any appropriate phase of manufacture, processing, or packaging of a particular drug product. *(also see: Theoretical Yield)*

Adenine (A) - A purine base, 6-aminopurine, occurring in RNA (ribonucleic acid) and DNA (deoxyribonucleic acid) and as a component of adenosine triphosphate. *(also see: Nucleic Acids)*

ADR - *see: Adverse Drug Reaction*

Adsorption - Adhesion of the molecules of a gas, liquid or dissolved substance to a surface because of chemical or electrical attraction - typically accomplished with granular activated carbon to remove dissolved organics and chlorine. The attachment of charged particles to the chemically active groups on the surface and in the pores of an ion exchanger.

Adventitious Agents - Acquired, sporadic, accidental contaminants.

Adverse Agents - Undesired effects or toxicity due to exposure (often but not limited to a drug or medical device).

Adverse Drug Reaction (ADR) - An undesirable effect that may be caused by a study drug.

Advisory Alarm - An alarm indicating a drift of a monitored parameter toward an out-of-spec condition. It is advisory in that no GMP violation has occurred, and is used to advise corrective action before an action alarm can happen.

Aerobe - An organism that can live and grow only in the presence of oxygen.

1. **Facultative aerobe:** one which normally thrives in the absence of oxygen, but which may acquire the faculty of living in the presence of oxygen.
2. **Obligate aerobe:** one that cannot live without air.

Aerobia - The plural of aerobe.

Aerobic - Living in air.

Aerobic Bacteria - Bacteria capable of growing in the presence of Oxygen.

Aerobion - *see: Aerobe*

Aerosol - A product that is dispensed by a propellant from a metal can up to a maximum size of 33.8 fluid ounces (1000 mL) or a glass or plastic bottle up to a size of 4 fluid ounces (118.3 mL), other than a rim-vented container.

Aerosol - A gaseous suspension of fine (100µm or smaller in size) solid or liquid particles.

Aerosol Photometer - Light-scattering mass concentration indicating instrument with a threshold sensitivity of at least 10 to the negative third power microgram per liter for 0.3µm diameter DOP (Dioctyl Phthalate) concentrations over a range of 10 to the fifth power times the threshold sensitivity. Photometers may include hand-held remote meter probes that can scan for airborne contaminants in HEPA filters, in penetrations around frames, seals and plenums, and in hoods and work stations.

AES - *see: Auger Electron Spectroscopy*

Agar - A complex mixture of polysaccharides obtained from marine red algae, used as an emulsion stabilizer in foods, as a sizing in fabrics, as a gelling agent and as a solid substrate or media for the laboratory culture of microorganisms. Agar melts at 100°C and when cooled below 44°C forms a stiff and transparent gel. Microorganisms are seeded and grown on the surface of the gel.

Agarose - A highly purified form of agar.

Agarose Gel Electrophoresis - A method used to separate, identify, and purify molecules of different molecular weight and/or structure. It is specifically applied to the separation of protein or DNA fragments where it is rapid, simple, and accurate, and the separated molecules can be visualized directly by staining with dyes. The electrophoretic migration rate of molecules through agarose gel is dependent on the following parameters:

1. **Molecular size:** molecules pass through the gel at rates that are inversely proportional to the log of their molecular weight.
2. **Agarose concentration:** a molecule of a given size migrates at different rates through gels containing different concentrations of agarose.
3. **Molecular conformation:** a molecule of the same molecular weight but of a different conformation will migrate at different rates. Generally, closed circular or globular forms will migrate faster than linear forms.
4. **Electric current:** at low voltages the rate of migration is proportional to the voltage, but as the voltage is increased the rate of migration of high molecular weight fragments is increased differentially.

(also see: Electrophoresis and Immuno Electrophoresis)

Agene - Nitrogen Trichloride (NCl_3).

Agglomerate - Suspended solids clustered together to form larger clumps or masses that are easier to remove by filtration or settling.

Agglutination - The sticking together of insoluble antigens such as bacteria, viruses or erythrocytes by a particular antibody. Agglutination assays are used to type human blood before a transfusion.

AHF (Antihemophilic Factor) - In the clotting of blood it is also known as Factor VIII. *(also see: Factor VIII)*

Airborne Particulate Cleanliness Classes - Statistically allowable number of particles equal to, or larger than 0.5µm in size per cubic foot of air. According to ISO 14644-1, a classification number, **N**, shall designate airborne particulate cleanliness. *(also see: Particle, and Table I, Section II – Comparison of Airborne Particulate Cleanliness Classes)*

Air Change Rate - The number of times the total air volume of a defined space is replaced in a given unit of time. This is computed by dividing the total volume of the subject space (in cubic feet) into the total volume of air exhausted from (or supplied to) the space per unit of time.

Air Cleaners - Filtration systems that may be freestanding or installed in a ceiling or wall to remove contaminants such as bacteria, viruses, and dust from the air. Air cleaners may incorporate HEPA filters.

Airflow Visualization - Using chemical smoke or fog to visualize flow patterns in a cleanroom or clean space.

Air-Lift Bioreactor - A reactor in which the source of agitation is air sparged upwards through a draft tube - most widely used for cell culture applications and monoclonal antibody production.

Airlock - A room or space designed to act as a means of segregating areas of different air classification or quality. It may contain a method to remove particulate contamination from clean room garments as personnel pass through, and usually includes HEPA filtered air supply and interlocking doors. Airlocks pressure will "float" between those of the spaces being protected. With all doors closed, the airlock pressure will be somewhere between that of the highest adjoining room and that of the lowest adjoining room as air flows through it from room to room. "Ventilated airlocks" are in neutral ducted air balance (supply CFM = return CFM).

Air Velocity Meters/Monitors - Meters to measure and indicate the force and speed of airflow. Meters may use a variety of probes for measuring near HEPA filters and at right angles. Monitors check and record air velocity.

Alarms - Audible or visual signals used to warn of unacceptable conditions at monitored sites. They may be buzzers, horns, speakers, bells, or warning lights. They can be Advisory, Alert, or Action alarms. The first two are for operation and maintenance information, to alert of abnormal situations that do not compromise product SISPQ. The Action alarm is for GMP records, indicating that product SISPQ *may* have been compromised, but Alert alarms are also usually recorded.

Albumin - Commonly, the white of egg is a simple protein widely distributed throughout the tissues and fluid of plants and animals. Soluble in pure water it is also precipitable from a solution by mineral acids, and coagulable by heat in acid or neutral solution.

Albuminoid - Resembling albumin, a simple protein present in horny and cartilaginous tissues, insoluble in neutral solvents. Keratin, elastin, and collagen are albuminoids. *(also see: Gelatin)*

Alert Point - Used in determining when a parameter is drifting toward extremes of the operating range.

Aliquot - Of, pertaining to, or designating an exact divisor or factor of a quantity, specially of an integer. To divide out a sample to multiple containers for multiple analytical tests.

Alkalinity - An expression of the total amount of basic anions (hydroxyl groups) present in a solution. In water analysis, it also represents the presence of carbonate, bicarbonate, and occasionally borate, silicate, and phosphate salts that react to produce hydroxyl groups. Bicarbonate and carbonate ions are expected to be in most waters. Hydroxide may occur in water that has been softened by the lime soda process or has been in contact with fresh concrete. Alkalinity furnishes a guide in choosing appropriate treatment of either raw water or plant effluents.

Allantoic Fluid - The clear white portion of an egg. In influenza vaccine manufacturing, the virus is propagated in the embryonic chick and sloughed into the allantoic fluid that is harvested to produce the vaccine.

Allele - Alternative form of a genetic locus; a single allele for each locus is inherited separately from each parent (e.g., at a locus for eye color the allele might result in blue or brown eyes). *(also see: Dominant Allele, and Recessive Allele)*

Allergenic Extract - An extract in a solvent of a substance that causes an allergic reaction. They are relative crude drugs by contemporary standards and are manufactured by specialty companies and in some cases, by a practicing allergist. Also, allergenic extracts are generally difficult to filter since they most frequently are extracts of natural substances such as foods, house dust, animal hair, etc.

Alum - Aluminum sulfate, commonly added during municipal water treatment to cause insoluble colloids to coalesce into larger particles that can be removed by settling. (*also see: Flocculation*).

Alzheimer's Disease - A disease that causes memory loss, personality changes, dementia and, ultimately, death. Not all cases are inherited, but genes have been found for familial forms of Alzheimer's disease.

Ambient - The normal environment conditions such as temperature, relative humidity, or room pressure of a particular area under consideration.

Ames Test - A simple bacterial test for carcinogens.

Amine - A substance that may be derived from ammonia by the replacement of one or more of the hydrogen atoms by hydrocarbon radicals.

Amino Acids - Any of a group of twenty hydrocarbon molecules (containing the radical group NH2) linked together in various combinations to form proteins in living things. Synthesized by living cells or obtained as essential components of the diet of human and animals, these twenty amino acids are divided into four (4) groups on the basis of their side-chain properties:

1. Neutral, hydrophobic side chains,
2. Neutral, hydrophilic side chains,
3. Acid, hydrophilic side chains,
4. Basic, hydrophilic side chains.

In addition to the twenty common amino acids there are less common derivatives (e.g. hydroxyproline, found in collagen) formed by the modification of a common amino acid.

Ampholyte - Amphoteric electrolyte. Electrolyte that can either give up or take on a hydrogen ion and can thus behave as either an acid or a base.

Amphoteric - Having two opposite characteristics.

Ampicillin - An antibiotic widely used in clinical treatment and rDNA research. It is a derivative of penicillin, which kills bacteria by interfering with the synthesis of the cell wall.

Amplification - An increase in the number of copies of a specific DNA fragment; can be *In Vivo* or *In Vitro. (also see: Clone)*

Amplification - The production of additional copies of a chromosomal sequence, found as either intrachromosomal or extrachromosomal DNA.

Ampoule or Ampule - A small glass vial sealed after filling and one of the earliest devices developed for safe storage of sterile injectable unit.

Amyotrophic Lateral Sclerosis - An inherited, fatal degenerative nerve disorder, also known as Lou Gehrig's disease.

Anabolism - The intracellular process involved in the synthesis of more complex compounds than those involved in catabolism (for example, glucose to glycogen) and requires energy. *(also see: Catabolism)*

Anaerobe - A microorganism that thrives best, or only, when deprived of oxygen.

1. **Facultative anaerobe:** one able to grow in the presence or absence of free oxygen.
2. **Obligate or obligatory anaerobe:** one that will grow only in the absence of free oxygen.

Anaerobic - Relating to an anaerobe.

Anaerobic Bacteria - Bacteria capable of growing in the absence of Oxygen.

Anaerobion - *(also see: Anaerobe)*

Analog - Pertaining to data that consists of continuously variable physical qualities.

Analytical Data Interchange (ANDI) - A generic file format. It was common practice before CFR 21 Part 11 to save information from analytical instruments in this file format. The disadvantage now is that the approach does not allow replaying of data on a different system to yield the same result.

Analytical Method - Small scale process used to characterize and/or separate a mixture, a compound, or an unknown material into its constituent parts or elements.

Ancillary Material - Material used in preparing drugs that does not become a component of the drug (e.g. steam, air, N2, DI water).

ANDI - *(also see: Analytical Data Interchange)*

Anemometer - A device that measures air speed.

Angstrom (Å) - A unit of length equal to one hundred-millionth of a centimeter (one ten-thousandth of a micron) used especially to specify radiation wavelengths.

Anion - A negatively charged particle or ion. *(also see: Ion)*

Anion Exchange Resin - An ion exchange material that removes anions from solution by exchanging them with hydroxyl ions.

Anneal - The process by which the complementary base pairs in DNA strands combine.

Annealing - A treatment process for steel in which the metal is heated and held at a suitable temperature and then cooled at a suitable rate for the purpose of reducing hardness, improving machinability, facilitating cold working, producing a desired microstructure, or obtaining desired mechanical, physical, or other properties.

Antibiotic - An organic substance of microbial origin (usually mold or actinomycete bacteria) that is either toxic or growth inhibiting for other organisms. Also with the advent of synthetic methods of production, a substance produced by a microorganism or a similar substance (produced wholly or partly by chemical synthesis) which, in low concentrations, inhibits the growth of other microorganisms. Penicillin, tetracycline, and erythromycin are examples of antibiotics.

Antibody - A modified protein molecule present in the blood serum or plasma (and other body fluids), whose activity is associated chiefly with gamma globulin. Produced by the immune system in response to exposure to a foreign substance, it is the body's protective mechanism against infection and disease. An antibody is characterized by a structure complementary to the foreign substance, the antigen that provokes its formation, and is thus capable of binding specifically to the foreign substance to neutralize it *(also see: Antigen)*.

Antigen - Any of various foreign substances such as bacteria, viruses, endotoxins, exotoxins, foreign proteins, pollen, and vaccines, whose entry into an organism induces an immune response (antibody production, lymphokine production, or both) directed specifically against that molecule. Response may be demonstrated as an increased reaction, such as hypersensitivity (usually protein or a complex of protein and polysaccharide, or occasionally a polysaccharide of high molecular weight), a circulating antibody that reacts with the antigen, or some degree of immunity to infectious disease if the antigen was a microorganism or its products.

Anti-interferon - An antibody to an interferon. Used for the purification of interferons.

Antiseptic - Acting against sepsis. An antiseptic agent is one that has been formulated for use on living tissue such as mucous membranes or skin to prevent or inhibit growth oraction of organisms. Antiseptics should not be used to decontaminate inanimate objects.

Antiserum - The blood serum obtained from an animal after has been immunized with a particular antigen. It contains antibodies specific for that antigen as well as antibodies specific for any other antigens with which the animal has previously been immunized.

Antistatic - Reducing static electric charges by retaining enough moisture to provide electrical conduction.

Antistatic Cleaners - Liquid cleaners that enhance surface conductivity of cleanroom tabletops, workstations, and other surfaces.

Antitoxin - An antibody that is capable of neutralizing the specific toxin that stimulated its production in the body. Antitoxins are produced in animals for medical purposes by injection of a toxin or toxoid, with the resulting serum being used to counteract the toxin in other individuals.

API (Active Pharmaceutical Ingredient) - Also called Drug Substance. Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that when used in the production of a drug becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

API Starting Material - A material used in the production of an API which is itself or is incorporated as a significant structural fragment into the structure of the API. A starting material may be an article of commerce, a material purchased from one or more suppliers under contract or commer cial agreement, or it may be produced in-house. Starting materials are normally of defined chemical properties and structure.

Apoenzyme - The protein moiety of an enzyme - determines the specifity of the enzyme reaction. *(also see: Enzyme)*

Application Software - Any executable program developed or modified specially for customer applications.

Appropriated login or Impersonation - Someone using the authorization code, usually user ID and password of another person to secure access to network resources for which he or she does not have privileges or authorization. Can be intentional or not. CFR 21 Part 11 mandates technical controls that prevent this.

Aquifer - An underground layer of permeable rock, sand, or gravel that contains water for wells or springs.

Arithmetic Average Roughness (R*a*) - The arithmetic average height of roughness component irregularities from the mean line measured within the sample length (L). This measurement conforms to ANSI/ASME B46.1 "Surface Texture - Surface Roughness, Waviness and Lay". **R*a*** (formerly known as AA or Arithmetic Average in the U.S., and CLA Centerline Average in the U.K.) is usually expressed in microinches (**µin**), and performed by moving a stylus or profilometer in a straight line along the surface. A consistent and measurable surface finish can be specified for a desired roughness i.e., 9-11 microinch. *(also see: Roughness)*

"As-Built" Cleanroom - ISO 14644-1 defines the "as built" occupancy state as "condition where the installation is complete with all services connected and functioning but with no production equipment, materials, or personnel present". *(also see: "At-Rest" Cleanroom, and "Operational" Cleanroom)*

Ascomycetes - A family of fungi marked by long spore-containing cells. Form sexual spores called ascospores, which are contained within a sac (a capsule structure). Ergot, truffles,

some molds of the genera *Neurospora* and *Aspergillus,* and yeasts belong to this category.

Asepsis - A condition in which living pathogenic (*causing or capable of causing disease*) organisms are absent.

Aseptic - Marked by or relating to asepsis.

Aseptic Processing - Processing conditions designed to achieve a sterile product.

Aseptic Processing Area - Area in which sterile product is formulated, filled into containers, and sealed.

Aseptic Transfer (in Isolators) - The key issue in all contained aseptic environments. Aseptic transfer is essential for change parts, components, and even product to enter and exit an isolator system without sterility challenges. There are an increasing number of ways to make an aseptic transfer. The following is a brief list of some of the key techniques:

1. **Alpha Beta Systems Double Door Systems:** also called RTPs (Rapid Transfer Ports) and HCT (High Containment Transfer). When mated, the two ports act as one door, protecting the internal and external environments.
2. **Alpha Beta Dry Heat Sterilized:** similar to Alpha Beta port with the additional safeguard of a heat sterilized seal.
3. **UV and Pulsed Light:** light sterilization/sanitization. Sterilizing the system by making use of a wide spectrum of light within the transfer chamber.
4. **One Shot Systems:** basically, two halves coming together. Similar to an Alpha Beta port but simpler, cheaper, and capable of only a single connection.
5. **Heat Welded Bag Systems:** passed in or passed out using a continuous polyethylene liner which is heat sealed and cut to maintain the integrity of the internal and external environments.
6. **Steam Sterilized:** the liquid component or powder path is clean steam sterilized after connection and prior to transfer.
7. **Autoclave/Depyrogenation/Dryheat:** pass through for batch. Use of conventional autoclave to sterilize a canister provided with an Alpha Beta port and filters to allow the passage of steam and safe aspiration on cooling. Depyrogenation/Dryheat uses dry heat to sterilize and at sufficient temperature depyrogenate components, typically glassware, in a batch oven
8. **Depyrogenation Tunnel:** standard volume glassware entry. Depyrogenation/Dry heat uses dry heat to sterilize and at sufficient temperature to depyrogenate components, typically glassware, in a tunnel allowing continuous input.

ASME Bioprocessing Equipment (BPE- 1997) - An American National Standard that covers, either directly or by reference, requirements for materials, design, fabrication, examination, inspection, testing, certification (for pressure systems), and pressure relief (for pressure systems) of vessels and piping for bioprocessing systems, including sterility and cleanability (Part **SD**), dimensions and tolerances (Part **DT**), surface finish requirements (Part **SF**), material joining (Part **MJ**), and equipment seals (Part **SG**) for the bioprocessing systems in which the pressure vessels and associated piping are involved. This Bioprocessing Equipment (BPE) Standard does not address all aspects of these activities, and those aspects that are not specifically addressed should not be considered prohibited.

Requirements of this Standard apply to:

1. All parts that contact the product, raw materials, and/or product intermediates during manufacturing, process development, or scale-up.
2. All equipment or systems that are critical part of product manufacture, such as Water For Injection (WFI), clean steam, ultrafiltration, intermediate product storage, and centrifuges.

ASME/ANSI B31 Code for Pressure Piping - A number of individually published Sections, each an American National Standard. Rules for each Section reflect the kinds of piping installations considered during its development, as follows:

1. **B31.1 Power Piping:** piping typically found in electric power generating stations, in industrial and institutional plants, geothermal heating systems, and central and district heating and cooling systems.
2. **B31.3 Process Piping:** piping typically found in petroleum refineries, chemical, *pharmaceutical*, textile, paper, semiconductor, and cryogenic plants, and related processing plants and terminals. Certain piping within a facility may be subject to other codes and standards, including but not limited to: (a) **ANSI Z223.1 National Fuel Gas Code:** piping for fuel gas from the point of delivery to the connection of each fuel utilization device. (b) **NFPA Fire Protection Standards:** fire protection systems using water, carbon dioxide, halon, foam, dry chemical, and wet chemicals. (c) **NFPA 99 Health Care Facilities:** medical and laboratory gas systems. (d) Building and plumbing codes, as applicable, for potable hot and cold water, and for sewer and drain systems.
3. **B31.4 Pipeline Transportation Systems for Liquid Hydrocarbons and Other Liquids:** piping transporting products that are predominately liquids between plants and terminals and within terminals, pumping, regulating, and metering stations.
4. **B31.5 Refrigeration Piping:** piping for refrigerants and secondary coolants.
5. **B31.8 Gas Transportation and Distribution Piping Systems:** piping transporting products that are predominately gas between sources and terminals, including compressor, regulating, and metering stations; gas gathering pipelines.
6. **B31.9 Building Services Piping:** piping typically found in industrial, institutional, commercial, and public buildings, and in multi-unit residences, which does not require the range of sizes, pressures, and temperatures covered in B31.1.
7. **B31.11 Slurry Transportation Piping Systems:** piping transporting aqueous slurries between plants and terminals and within terminals, pumping, and regulating stations.

Assay - A technique (test) for measuring a biological response or for determining characteristics such as composition, purity, activity, and weight.

Assimilation - The formation of cellular material utilizing small food molecules and energy.

Atmospheric Tank (Fire Code) - A storage tank designed to operate at pressures from atmospheric through 0.5 pounds per square inch (psig) (3.4 kPa).

Atomic Absorption Spectrophotometry - A highly sensitive instrumental technique for identifying and measuring metals in water.

At Rest - HVAC room condition when unmanned, and without machinery operating. Previously called "static condition".

"At-Rest" Cleanroom - ISO 14644-1 defines "at rest" occupancy state as "condition where the installation is complete with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present".

European Community (EC) defines "at rest" state as "the condition where the installation is complete with production equipment installed and operating but with no operating personnel present". The Medicines Inspectorate, however, further clarifies, "It should normally be taken to mean that ventilation systems are operating and other equipment is present in an operational condition but not in use". *(also see: "As-Built" Cleanroom, and "Operational" Cleanroom)*

Audit Comment - A feature of the audit trail that aids both originator and reviewer in understanding why the originator performed a specific action. CFR 21 Part 11 does not require entering the reason for a record change, but some predicate rules (such as GLPs) do expect an explanation. It is important that the user interface for entering audit comments prevents users from changing the audit trail itself.

Audit Trail - A computer-generated and time-stamped record of who did what, when. CFR 21 Part 11 requires audit trails to be generated independently of operators. An audit trail must capture all activities related to creating, modifying, and destroying records on a system.

Auger Electron Spectroscopy (AES) - An alternative surface analysis that can detect all elements with an atomic number greater than that of helium with the additional ability to analyze sub micron-diameter features. It is not as quantitative as ESCA and cannot determine the chemical state of an element. The primary advantage of Auger is that when combined with etching, a chemical depth profile can be measured rapidly and can image the distribution on the surface of spatial limitation resolution of 100 to 1,000 angstroms (depending on the equipment capability).

Austenite - A face-centered cubic crystal with high solubility for carbon (about 2%); an allotropic form of iron resulting from steel being heated above the transformation temperature.

Autegoneous Weld - A weld made by fusion of the base material without the addition of filler. (*also see: Gas Tungsten Arc Welding*)

Authentication - The process of identifying a person, system, or company sufficiently to allow access to a system or part of a system.

Authentication Mechanisms - Also known as authority checks, or authorized signers are mechanisms distinct from authorization that grants or denies access to a network resource, authentication programs are used by system administrators to establish and verify as conclusively as possible that a person logging in to the network is who he or she claims to be. FDA says that "authority checks" are to "ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system, input or output device, alter a record, or perform operations".

Authority Checks - *(also see: Authentication Mechanisms)*

Authorized Signers - *(also see: Authentication Mechanisms)*

Autoclave - An apparatus into which moist heat (steam) under pressure is introduced to sterilize or decontaminate materials placed within (e.g. filter assemblies, glassware, etc.). Steam pressure is maintained for pre-specified times and then allowed to exhaust. There are two types of autoclaves:

1. **Gravity displacement autoclave:** this type of autoclave operates at 121°C. Steam enters at the top of the loaded inner chamber, displacing the air below through a discharge outlet.
2. **Vacuum autoclave:** this type of autoclave can operate with a reduced sterilization cycle time. The air is pumped out of the loaded chamber before it is filled with steam.

Auto Immune Disease - A disease in which the body produces an immunogenic response against self-antigens. In some cases, predominantly one organ is affected (e.g. hemolytic anemia and chronic thyroiditis); in others, the disease process is diffused through many tissues (e.g. SLE (Systemic Lupus Erythematosis)).

Automated System - Any facility system or piece of equipment that is controlled with limited or no manual intervention.

Automatic Welding - Welding with equipment that performs the welding operation without adjustment of the controls by a welding operator. The equipment may or may not perform the loading and unloading of the work.

Autoradiography - A technique that uses X-ray film to visualize radioactively labeled molecules or fragments of molecules; used in analyzing length and number of DNA fragments after they are separated by gel electrophoresis.

Autosome - A chromosome not involved in sex determination. The diploid human genome consists of 46 chromosomes, 22 pairs of autosomes, and 1 pair of sex chromosomes. *(also see: Sex Chromosomes)*

Autotrophs - One of two categories in which microorganisms are classified on the basis of their carbon source. Autotrophs use carbon dioxide as a carbon source. *(also see: Chemoautotrophs, Photoautotrophs, and Heterotrophs)*

- B -

BAC (Bacterial Artificial Chromosome) - A vector used to clone DNA fragments (100-kb to 300-kb insert size; average, 150-kb) in E. Coli cells. Based on naturally occurring F-factor plasmid found in the bacterium E. coli. *(also see: Cloning Vector)*

Background Contamination - Contamination introduced accidentally in reagents, dilution water, solvents, rinse water, etc., which can be confused with constituents in samples being analyzed.

Background Environment - The environment that surrounds a critical area.

Back-up Copy - A magnetic copy of data, software, user-developed application, or operating parameters associated with an automated system and not considered the original.

Backward Compatibility - A new version of a computer program that can use files and data created with an older version of the same program. A computer is said to be backward compatible if it can run the same software as the previous model. Backward compatibility is important because it eliminates the need to start over when you upgrade to a newer product, but is sometimes sacrificed in favor of a new technology. *(also see: Upward Compatibility)*

Backwash - The countercurrent flow of water through equipment, usually to clean or to recover performance, such as in a resin bed (flow-in at the bottom of the exchanger unit and out at the top) to clean and reclassify the bed after exhaustion. This process of reversing flow may also be applied to filters in order to force contaminants out of plugged pores and passages.

Bacteria - The plural of Bacterium.

Bactericide - An agent that kills vegetative bacteria but not mycobacteria or spores.

Bacteriophage - A virus that exclusively infects bacteria. A protein coat surrounds the genome (DNA or RNA). One of the bacteriophages most extensively studied is the lambda phage, which is also one of the most important viral vectors used in rDNA work. Lambda promoters have been used to express eukaryotic proteins in *E.coli*. *(also see: Phage)*

Bacteriostatic - Inhibiting growth of bacterial organisms without necessarily killing them or their spores.

Bacteriostatic Water For Injection, U.S.P. - Water that serves the same purposes as Sterile Water for Injection, it meets the same standards, with the exception that it may be

packaged in either single-dose or multiple-dose containers of not larger than 30-mL size. *(also see: Water For Injection (WFI), U.S.P.)*

Bacterium - Any of a large group of microscopic organisms having round, rod-shaped, spiral, or filamentous unicellular or noncellular bodies that are often aggregated into colonies, are enclosed by a cell wall or membrane (prokaryotes), and lack fully differentiated nuclei. Bacteria range in size from 0.4µm to 2.0µm and may exist as free-living organisms in soil, water, organic matter, or as parasites in the live bodies of plants. Some are disease producing, but most perform necessary functions such as digestion, fermentation, and nitrification. Most of the forms are variously grouped under generic names such as: *Alcaligenes, Dialister, Escherichia, Klebsiella, Kurthia, Pasteurella, Salmonella, and Shigella*.

Barometer - Instrument used to measure atmospheric pressure.

Barrier Isolator - A containment device that utilizes barrier technology for the enclosure of a controlled workspace. There are two main types of isolator:

1. **Type 1 Isolator:** An isolator designed to protect the product from process-generated and external factors that would compromise its quality.
2. **Type 2 Isolator:** An isolator designed to protect the product from process-generated and external factors that would compromise its quality and to protect the operator from hazards associated with the product.

(*also see: Isolator*)

Barrier Technology - The technology of using separating environments, whether protecting the world from a product or the product from the world. Containment, barrier isolation and isolation all refer to the same technology, which is enclosing an environment. There are, however, some redefining terms that are gaining favor:

1. **Containment:** protect the world from the product (as in the case of highly potent compounds or a toxic).
2. **Isolation:** protect the product from the world (as in the case of a sterile product).
3. **ISO 14644-7:** "Minienvironments and Isolators" will define further levels of devices

Base - An electropositive element or radical that unites with an acid to form a salt. Or, a substance that when dissolved in water, dissociates to produce one or more hydroxyl ions (OH).

Base Pair (bp) - Two nucleotides that are in different nucleic acid chains and whose bases pair by hydrogen bonding. In DNA, the nucleotide bases are adenine (A) that always pairs with thymine (T) and guanine (G) which pairs with cytosine (C). In RNA molecules, adenine (A) joins the uracil (U). Two strands of DNA are held together in the shape of a double helix by the bonds between these pairs.

Base Sequence - The order of nucleotide bases in a DNA molecule.

Base Sequence Analysis - A method, sometimes automated, for determining the base sequence.

Baseline - In some analytical procedures a sample is dissolved in water or combined with other reagents for analysis. A "blank" or standard consisting of the same reagents may be analyzed without sample present. This provides a comparative reference point, or baseline, so that the test results can be attributed solely to the sample itself.

Baseline® Pharmaceutical Engineering Guides (ISPE) - A series of industry publications developed in partnership with the US Food and Drug Administration (FDA). Each volume in the series is a collaborative effort of industry leaders representing a broad cross-section of manufacturers and other industry experts. The Guides document current industry practice for facilities and systems used for production of pharmaceutical products and medical devices. They are intended to:

- Establish a baseline approach to new and renovated facility design, construction, commissioning, and qualification that is based upon clear understanding of the type of product and its manufacturing process.
- Prioritize facility design features based upon the impact on product and process.
- Avoid unnecessary spending on facility features that do not contribute to consistent production of quality products.

The Guides include five product manufacturing operation based guides (vertical guides), and three support system/function based guides (horizontal guides):
Volume 1: Bulk Pharmaceutical Chemicals (June 1996)
Volume 2: Oral Solid Dosage Forms (February 1998)
Volume 3: Sterile Manufacturing Facilities (January 1999)
Volume 4: Water and Steam Systems (January 2001)
Volume 5: Commissioning and Qualification (March 2001)
Volume 6: Biotech (in progress)
Volume 7: Packaging and Warehousing(in progress)
Volume 8: Oral Liquids and Aerosols(in progress)

Basidiomycetes - Reproduce by basidiospores, which are extended from the stalks of specialized cells called the basidia. The class comprises *Photobasidiomycetes* (smuts and rusts) and the *Hymenomycetes* (mushrooms and puffballs).

Basis of Design - A design document that describes what the purpose of a given system is and how the system will accomplish its required task. This document is created and approved before the issuance of bid specifications and is often used to develop them. Until the system is developed this is a conceptual document.

Batch - A specific quantity of material produced in a process or series of processes so that is expected to be homogeneous within specified limits. In the case of continuous production a batch may correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size may be defined either by fixed quantity or the amount produced in a fixed time interval.

Batch Number - A unique combination of numbers and/or letters which specifically identify a batch or lot and from which the production and distribution history can be determined.

Batch Fermentation - The process in which a fixed volume of sterile medium in a vessel is inoculated with a desired organism. The broth is fermented for a defined period to completion, without further additions of media. After discharging the batch, the fermenter is cleaned and rebatched with medium for another cycle. Two other types of fermentation cycles are fed batch and continuous.

Batchwise Control - The use of validated in-process sampling and testing methods such that results prove the process has done what it purports to do for the specific batch concerned, assuming control parameters have been appropriately maintained.

Bed - Column of carbon, sand, chromatography, or ion exchange resins through which a liquid passes during operation.

Bed Depth - The height of the exchange or capture material in a column after proper backwashing for effective operation.

Bed Expansion - The effect produced during backwashing; resin particles separate and rise in the column. Regulating backwash flow may control bed expansion caused by the increase in space between resin particles.

Binary Explosive - An explosive material composed of separate components, each of which is safe for storage and

transportation and would not in itself be considered as an explosive.

Bioactivity - A protein's ability to function correctly after it has been delivered to the active site of the body (in vivo).

Bioassay - The determination of the biological activity of a substance (e.g. a drug) by observing its effect on an organism (or organ) compared to a standard preparation.

Bioaugmentation - A strategy involved in bioremediation that increases the activity of an organism to break down or metabolize a pollutant. This involves reseeding a waste site with bacteria as they die.

Bioburden - The level and type of microorganisms which may be present in raw materials, API (Active Pharmaceutical Ingredient) starting materials, intermediates, or APIs which have defined limits and should not affect the quality of the API. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Biochemical Oxygen Demand (BOD) - *(also see: BOD (Biochemical Oxygen Demand))*

Biochemistry - The study of chemical processes in living things. Despite the dramatic differences in the appearance of living things, the basic chemistry of all organisms is strikingly similar. Even tiny, one-celled creatures carry out essentially the same reactions that each cell of a complex organism, such as man, carries out.

Biocide - An agent that can kill all pathogenic and non-pathogenic living organisms, including spores. More general than bacteriocide, biocide includes insecticides and any compound toxic to any living thing.

Biodegradable - Material that can be broken down by biological action.

Bioequivalency - A scientific basis on which generic and brand name drugs are compared with one another. Drugs are bioequivalent if they enter circulation at the same rate when given in similar doses under similar conditions.

Biogenerator - A contained system, such as a fermentor, into which biological agents are introduced along with other materials so as to effect their multiplication or their production of other substances by reaction with the other materials. Biogenerators are generally fitted with devices for regulation, control, connection, material addition, and material withdrawal. *(also see: Fermenter)*

Biohazard - An infectious agent(s), or part thereof, presenting a real or potential risk to human, other animals, or plants, directly through infection or indirectly through disruption of the environment.

Bioinformatics - The use of computers in the life sciences, electronic databases of genomes and protein sequences, and computer modeling of biomolecules and biologic systems.

Biologic - A therapeutic agent derived from living things.

Biological Barrier - An impediment (naturally occurring or introduced) to the infectivity and/or survival of a microbiological agent or eukaryotic cell once it has been released into the environment.

Biological Impurities - Impurities resulting from living matter (bacteria, virus, algae, protozoa, microfungi) and their by-products, including pyrogens (endotoxins).

Biological Indicators - Resistant microorganisms placed into or on various materials to confirm that a sterilization process is effective. They may for instance be placed within a filter in order to determine if a proposed autoclave cycle is effective. After autoclave, they are removed and culture tests are performed to see if the microorganisms were killed.

Biological Oxygen Demand (BOD) - *(also see: BOD (Biological Oxygen Demand))*

Biological Reactivity Tests, In Vivo - This classification is based on responses to a series of in vivo tests for which extracts, materials and routes of administration are specified. Six Plastic Classes are defined:

1. **Class I:** Uses a specified dosage of an extract of sample in Sodium Chloride Injection applied either intravenously or intracutaneously into a mouse or a rabbit.
2. **Class II:** Same as Class I but in addition uses an extract of sample in 1 in 20 Solution of Alcohol in Sodium Chloride Injection applied either intravenously or intracutaneously into a mouse or a rabbit.
3. **Class III:** Same as Class II but in addition uses an extract of sample in Polyethylene Glycol 400, and an extract of sample in Vegetable Oil, both applied either intraperitoneally or intracutaneously into a mouse.
4. **Class IV:** Same as Class II but in addition uses an extract of sample in Vegetable Oil applied intraperitoneally or intracutaneously into a mouse or a rabbit. Also uses implant strips of sample into a rabbit.
5. **Class V:** Same as Class II but in addition uses an extract of sample in Polyethylene Glycol 400, and an extract of sample in Vegetable Oil applied intraperitoneally or intracutaneously into a mouse or a rabbit.
6. **Class VI:** Same as Class V but in addition uses implant strips of sample into a rabbit.

These tests are designed to determine the biological response of animals to elastomerics, plastics and other polymeric material with direct or indirect patient contact, or by the injection of specific extracts prepared from the material under test. Three tests are described:

1. **Systemic Injection Test:** Designed to determine the systemic biological responses of animals to plastics and other polymers by the single-dose injection of specific extracts prepared from a sample.
2. **Intracutaneous Test:** Designed to determine the local biological responses of animals to plastics and other polymers by the single-dose injection of specific extracts prepared from a sample.
3. **Implantation Test:** Designed to evaluate the reaction of living tissue to the plastic and other polymers by the implantation of the sample (specimen under test) itself into animal tissue.

With the exception of the Implantation Test, the procedures are based on the use of extracts that, depending on the heat resistance of the material, are prepared at one of the three standard temperatures: 50°, 70°, and 121°. Therefore, the class designation of a plastic must be accompanied by an indication of the temperature of extraction e.g., IV - 121°, which represents a class IV plastic extracted at 121°).
(also see: Plastics U.S.P. Classification)

Biological Safety Cabinets (BSCs) - Bench-top or freestanding cabinets with unidirectional airflow used for handling materials that present a health hazard. The National Institutes of Health (NIH) Guidelines classify them as:

1. **Class I:** A negative pressure, ventilated cabinet for personnel protection having an inward flow of air away from the operator. The exhaust air is filtered through a HEPA filter (located at rear or top) either into the laboratory or to the outside. This cabinet is designed for general microbiological research with low and moderate risk agents (BL-2 and BL-3 agents), and is used in three operational modes:
   a) With a full width open front. The face velocity of the inward flow of air through the full width open front is at least 75' feet per minute.
   b) With an installed front closure panel (having four 6-inch diameter openings) without gloves. The face veloc-

ity of the inward flow of air through the openings will increase to approximately 150' feet per minute.

c) With an installed front closure panel equipped with arm-length rubber gloves, and inlet air pressure relief for further protection. In this configuration, it is necessary to install a make-up air inlet fitted with a HEPA filter in the cabinet.

2. **Class II:** A ventilated cabinet for personnel and product protection having an open front with inward airflow for personnel protection (75' to 100' feet per minute), and HEPA filtered downward unidirectional airflow for product protection. The exhaust air is filtered through a HEPA filter for environmental protection. For selection and procurement of Class II cabinets refer to standards developed by the National Sanitation Foundation, Ann Arbor, Michigan. Cabinets are further classified as:
   a) **Type A:** Suitable for microbiological research in the absence of volatile or toxic chemicals and radionuclides (BL-2 and BL-3), with 70% recirculated air through HEPA. They are exhausted through HEPA into the laboratory or to the outdoors via a "thimble" connection to the building exhaust system.
   b) **Type B:** Hard ducted to the building exhaust system, contains negative pressure plena, and face velocity of 100' feet per minute. Type B cabinets are further subtyped into types: **B1** (30% recirculated air through HEPA; exhaust via HEPA and hard ducted. BL2 and BL-3), **B2** (No recirculation; total exhaust via HEPA and hard ducted. BL-2 and BL-3), and **B3** (same as IIA, but plena under negative pressure to room and exhaust air is ducted. BL-2 and BL-3).

   Classes I and II should be located away from traffic patterns and doors, airflow from fans, room air supply louvers, and other air moving devices.

3. **Class III:** Closed-front ventilated cabinet of gas tight construction that provides the highest level of personnel protection from infectious aerosols, as well as protection of research materials from microbiological contaminants. The interior of the cabinet is protected from contaminants exterior to the cabinet. The cabinet is fitted with arm-length rubber gloves and is operated under negative pressure of at least 0.5 inches water gauge. All supply air is filtered through HEPA filters. Exhaust air is filtered through two HEPA filters in series or one HEPA filter and incinerator before being discharged to the outside environment. Class III cabinets are most suitable for work with hazardous agents that require Biosafety Level 3 or 4 containment. Cabinets must be connected to a double-door autoclave and/or chemical dunk tank used to sterilize or disinfect all materials exiting the cabinet, and to allow supplies to enter the cabinet. *(also see: Positive Pressure Personnel Suit)*

(also see: Containment, Biosafety Level)

Biologics - "Any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product… applicable to the prevention, treatment, or cure of diseases or injuries of man…"

Biomass - Organic matter grown by the photosynthetic conversion of solar energy.

Biomass - The entire assemblage of living organisms (both plant and animal), of a particular region, considered collectively.

Biometabolism - Physical and chemical processes that occur within a cell or an organism, for example, the conversion of nutrients into energy.

Biometrics - A method of verifying an individual's identity based on measurement of his/her physical feature(s) or repeatable action(s) where those features and/or actions are both measurable and unique to that individual. The main types of biometrics are: face recognition, finger scanning, hand geometry, finger geometry, iris recognition, palm, retina, signature, and voice recognition.

Bionics - An interscience discipline for constructing artificial systems, which resemble or have the characteristics of living systems.

Biopharmaceuticals - Ethical pharmaceutical drugs derived through bioprocessing.

Bioprocessing - The creation of a product utilizing a living organism.

Bioprocess Engineering - Process that uses complete living cells or their components (e.g., enzymes, chloroplast) to effect desired physical or chemical changes.

Biopsy - The gross and microscopic examination of tissues or cells removed from a living patient, for the purpose of diagnosis or prognosis of disease, or for the confirmation of normal conditions.

Biopure Water - Water that is sterile, pyrogen free and has a total solids content of less than 1 ppm.

Biosphere - All the living matter on or in the earth, the oceans and seas, and the atmosphere.

Bioreactor - A closed system used for bioprocessing (flask, roller bottle, tank, vessel, or other container), which supports the growth of cells, mammalian or bacterial, in a culture medium. A bacterial reaction usually is said to take place in a fermenter, and cell culture in a bioreactor.

Biosafety Level - The National Institutes of Health (NIH) specifies physical containment levels and defines Biosafety Levels in their "Guidelines for Research Involving Recombinant DNA Molecules" - Appendix G - May 1999. There are four biosafety levels for operations performed with infectious agents:

1. **BL1:** Practices, safety equipment, and facilities appropriate for work performed with defined and characterized strains of viable microorganisms not known to cause disease in healthy adult humans. The **Basic Laboratory**. This laboratory provides general space in which work is done with viable agents that are not associated with disease in healthy adults. Conventional laboratory designs are adequate. Areas known to be source of general contamination, such as animal rooms and waste staging areas, should not be adjacent to patient care activities. Public areas and general offices to which non-laboratory staff requires frequent access should be separated from spaces, that primarily support laboratory functions.
2. **BL2:** Practices, safety equipment, and facilities appropriate for work performed with a broad spectrum of moderate risk agents present and associated with human disease of varying severity. The **Basic Laboratory**. This laboratory provides general space in which work is done with viable agents that are not associated with disease in healthy adults. Conventional laboratory designs are adequate. Areas known to be sources of general contamination, such as animal rooms and waste staging areas, should not be adjacent to patient care activities. Public areas and general offices to which non-laboratory staff requires frequent access should be separated from spaces, which primarily support laboratory functions.
3. **BL3:** Practices, safety equipment, and facilities appropriate for work performed with indigenous or exotic agents where the potential for infection by aerosols is real and the

disease may have serious or lethal consequences. Just walking through the area and breathing the air could infect one. The **Containment Laboratory**. This laboratory has special engineering features that make it possible for laboratory workers to handle hazardous materials without endangering themselves, the community, or the environment. The unique features that distinguish this laboratory from the basic laboratory are the provisions for access control and a specialized ventilation system. The containment laboratory may be an entire building, a single module, or complex of modules within a building. In all cases, a controlled access zone from areas open to the public separates the laboratory.

4. **BL4:** Practices, safety equipment, and facilities appropriate for work performed with dangerous and exotic agents that pose a high individual risk of life-threatening disease. Exposure to the skin could cause infection. The **Maximum Containment Laboratory**. This laboratory has special engineering and containment features that allow activities involving infectious agents that are extremely hazardous to the laboratory worker or that may cause serious epidemic disease to be conducted safely. Although the maximum containment laboratory is generally a separate building, it can be constructed as an isolated area within the building. The laboratory's distinguishing characteristic is that it has secondary barriers to prevent hazardous materials from escaping into the environment. Such barriers include sealed openings into the laboratory, airlocks or liquid disinfectant barriers, a clothing-change and shower room contiguous to the laboratory, a double door autoclave, a biowaste treatment system, and a treatment system to decontaminate exhaust air.

(*also see: Good Large Scale Practice, Containment Level, and Table II, Section II - Comparison of Good Large Scale Practice (GLSP) and Biosafety Level (BL) - Large Scale (LS) Practice)*

Biosynthesis - The production, by biological synthesis or degradation, of compounds by a living organism (e.g. amino acid synthesis, nucleotide synthesis).

Biotechnology - An industry that creates, develops, and markets a variety of techniques that use living organisms, or substances from those organisms, to make or modify a product by microbial and biochemical processes. A common misconception is that biotechnology refers only to recombinant DNA or gene splicing work. Recombinant DNA is only one of the many techniques used to derive products for organisms, plants, and parts of both for the biotechnology industry. A list of areas covered by the term biotechnology would more properly include: plant tissue culture, cell fusion techniques (especially for the production of monoclonal antibodies), enzyme systems, plant breeding, meristem culture, fermentation, and others.

Biotechnology - A process of applying genetic engineering (recombinant DNA), hybrid (monoclonal antibody), hybridization (gene probes), bioelectric, etc. to commercial applications in pharmaceutical, chemical, medical diagnostic device, food, animal and plant industries.

Biotechnology Products - Large molecules that are not manufactured by means of chemical synthesis but rather produced by means of fermentation and/or recovery, sourced from genetically engineered products.

Biowaste Inactivation - The inactivation or "killing" of biological organisms using heat or chemicals. This step is done at the end of the processing to ensure that there are no living organisms remaining in the effluent that is sent to the sanitary sewer system. Heat is usually applied at 130°C (266°F) for mammalian cells. Chemicals used include caustic or acid.

BLA (Biologics License Application) - The required application for marketing a biologic product in the United States. Most biopharmaceuticals are biologics.

Blank - A preliminary analysis omitting only the sample to provide an unbiased reference point or baseline for comparison. It is important to minimize extraneous contamination that could be confused with constituents in the sample itself.

Blind Weld - A "blind weld" is defined as a pipe or tube joint welded automatically in which there is no physical way to inspect the weld either visually or with a borescope.

Blinding - Clinical trial technique in which, to eliminate bias in a research study, subjects and/or clinical investigators remain unaware of which investigational product is provided. (*also see: Double Blind Test*)

Blood-Borne Pathogens - Infectious microorganisms that are carried in the blood of infected humans or animals and that can be transmitted through contact with infected blood, body fluids, tissues, or organs. Blood-borne pathogens are implicated in diseases such as malaria, syphilis, brucellosis, tuberculosis, hepatitis B, and AIDS (Acquired Immunodeficiency Syndrome). Workplace transmission of a blood-borne pathogen can occur via accidental inoculation with a contaminated "sharp" exposure through open cuts, skin abrasions, and mucous membranes of eyes and mouth indirect transmission (e.g., touching mouth, eyes, nose or open cuts with contaminated hands).

Blood Corpuscle - A cell that circulates in the blood.

Blood Plasma - Blood from which all blood corpuscles, with the exception of platelet cells, have been removed (e.g. by centrifugation) resulting in a clear, straw-colored fluid, which clots as easily as whole blood.

Blood Platelets - Small, disc-shaped, metabolically active cells circulating in the blood. They are essential in the blood clotting process since they aggregate to form a plug on the injured surface of the blood vessel.

Blood Serum - The liquid expressed from clotted blood or clotted blood plasma.

Blowdown - The bleeding-off of fixed quantities of accumulated feed water to reduce concentrated impurities. If these impurities are permitted to accumulate, they may pass through the distillation process and contaminate the distillate or foul the distillation system.

Blowdown - The withdrawal of water from an evaporating water system to maintain a solids balance within specified limits of concentration of those solids.

Blow (Form) Fill, Seal - Refers to machines that combine formation of a plastic container by blow molding, aseptic filling of a liquid product and sealing of the final package. In the U.S., a major company is ALP, or Automatic Liquid Packaging (Weiler Engineering) and in Europe, Rommilog.

BME (Basic Medium Eagles) - One of the most common tissue culture media composed of isotonic salts, carbohydrates and vitamins. When combined with animal serum. BME is a good medium for cell proliferation. *(also see: Fetal Calf Serum)*

BOD (Biochemical Oxygen Demand) - The amount of oxygen required to oxidize the dissolved organic matter in a water sample by aerobic (bacterial) decay. A measure of the oxygen depletion that would result from discharging organic impurities into a waterway.

BOD (Biological Oxygen Demand) - The oxygen used in meeting the metabolic needs of aerobic organisms in water containing organic compounds. *(also see: BOD (Biochemical Oxygen Demand))*

bp - *(also see: Base Pair)*

BPC (Bulk Pharmaceutical Chemical) - A pharmaceutical product derived by chemical synthesis, in bulk form, for later dispensing, formulation or compounding, and filling in a pharmaceutical finishing facility.

Breakthrough - Passage of a substance through a bed, filter, or process designed to eliminate it. For ion exchange processes, the first signs are leakage of ions (in mixed beds, usually Silica) and the resultant increase in conductivity. For organic removal beds, usually small, volatile compounds (Trihalomethanes (THMs) are common in activated carbon).

BSE (Bovine Serum Albumin) - A blood protein that makes up approximately 55-65% of the proteins in the bovine serum. Used as a size marker on gels and as carrier protein.

BSE (Bovine Spongiform Encephalopathy) - Sometimes called "Mad Cow Disease". A disease of cattle presumably caused by a virus or other unidentified entity that affects the brain and causes the cow to behave erratically. Prevalent in parts of Europe but not in the United States. BSE is a contaminant that is undesirable in bovine sera. It is not known whether the causative agent can be filtered out since the causative agent itself is not known. In humans, it is believed to cause *Creutzfeld-Jacob*, a disease affecting the nervous system.

BVD (Bovine Viral Diarrhea) - Viral contaminant found in bovine sera. Able to be filtered out using 0.1 µm nylon filters.

Bovine - Of, relating to, or from a cow: *such as Bovine Blood: blood from a cow*.

Braze Welding - A welding process using nonferrous filler metal that has a melting point below that of the base metals, but above 427°C (800°F). The filler metal is not distributed in the joint by capillary attraction. This type of welding has been also called Bronze welding, a misnomer.

Brazing - A metal joining process wherein coalescence is produced by use of a nonferrous filler metal having a melting point above 427°C (800°F), but lower than that of the base metals being joined. The filler metal is distributed between the closely fitted surfaces of the joint by capillary action.

Breakthrough - The first appearance in the effluent of an ion-exchange unit of unadsorbed components similar to those that deplete the activity of the resin bed. Breakthrough indicates that the resin is exhausted and needs to be regenerated.

Breath Control Shields - Typically made of acrylic or plastic materials, shields protect product, equipment, or the work from particulate contamination expelled by people.

Broad Spectrum - Over a wide range. A broad-spectrum disinfectant is effective against a wide range of microorganisms including bacterial spores, mycobacteria, non-lipid and lipid viruses, fungi, and vegetative bacteria.

Broth - The liquid culture medium in which fermentation or cell culture takes place.

Bronze Welding - *(also see: Braze Welding)*

Btu (British thermal unit) - The unit used to measure the amount of heat in a substance. One Btu is the heat required to produce a temperature rise of 1°F. in one lb. of water.

Bubble Point Test - A filter leakage test in which the filter is wetted and air pressure is applied and slowly increased until water is expelled from the largest pores and bubbles appear from a submerged tube in a downstream collection vessel. Vigorous bubbling, as opposed to a diffusional airflow or occasional bubbles, is indicative of reaching the bubble point. This visual test can be fairly accurate for low area filters, such as discs. When used to evaluate high area filters, it is subject to limitations in observation, test time, collection conditions, and pressurization rates. The bubble point test is not recommended for integrity testing of filter cartridges.

Buffer - A substance capable of neutralizing both acids and bases in solution, thereby maintaining the original acidity or causticity of the solution.

Buffer Prep Area - Section of most biotech facilities devoted to the preparation of controlled bioburden buffer solutions for use in the chromatographic separation area of those facilities.

Building Code - *(also see: Uniform Building Code)*

Building Occupancy Classification (California Building Code) - Every building, whether existing or to be erected, is classified by the building official according to its use or the character of its occupancy. The occupancy groups are as follows:

1. **Group A:** Assembly *(Section 303.1.1)*
2. **Group B:** Business *(Section 304.1)*
3. **Group C:** Organized Camp *(Section 431A)*
4. **Group E:** Educational *(Section 305.1)*
5. **Group F:** Factory and Industrial *(Section 306.1)*
6. **Group H:** Hazardous *(Section 307.1) (also see: Hazardous Occupancy - Group H)*
7. **Group I:** Institutional *(Section 308.1)*
8. **Group M:** Mercantile *(Section 309.1)*
9. **Group R:** Residential *(Section 310.1)*
10. **Group S:** Storage *(Section 311.1)*
11. **Group U:** Utility *(Section 312.1)*

Bulk Handling - The transferring of flammable or combustible liquids from tanks or drums into smaller containers for distribution.

Bulk Oxygen System - An assembly of equipment, such as storage containers, pressure regulators, safety devices, vaporizers, manifolds, and interconnecting piping that has a storage capacity of more than 12,000 cubic feet (340 m^3) of oxygen at normal temperature and pressure, connected in service or ready for service, or more than 25,000 cubic feet (708 m^3) of oxygen, including unconnected reserve on hand at the site.

Bulk Pharmaceutical Chemical (BPC) - *(also see: BPC (Bulk Pharmaceutical Chemical))*

Byte - An abbreviation for binary term. A storage unit capable of holding eight bits or the space required for a single letter or number, a single character.

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Airlocks for Biopharmaceutical Plants

by Manuel A. del Valle, PE

Introduction

In pharmaceutical and biopharmaceutical plants, airlocks are critical separation barriers between areas of different environmental air cleanliness classifications and between containment and non-containment areas. Airlocks may also operate as equipment "pass-thru", gowning areas, or de-gowning areas. Basically, airlocks help maintain air pressurization differentials and directional air flow between adjacent areas when personnel or equipment pass between these areas.

This article covers the following parameters affecting the design and operation of airlocks.

- various types of airlocks and their application
- air cleanliness classification and related air changes per hour (AC/HR) flow rates
- general materials of construction
- pressurization levels and the pressurization CFMs to accomplish these levels
- air distribution schemes
- air balancing methods
- temperature and pressure control

Types of Airlocks and their Application

Figure 1 shows four different types of airlocks:

- the "Cascading Pressure" airlock
- the "Pressure Bubble" airlock
- the "Pressure Sink" airlock
- the "Potent Compound" airlock

The Cascading Pressure Airlock is used to separate clean areas of different cleanliness or clean areas from non-classified areas. In operation, pressurization air "cascades" from the cleanest to the less clean adjacent area, allowing air from the clean area to flow into the less clean area through door or wall cracks or wall openings and prevents particles or dirt from the less clean area from entering the cleaner area. In this application the same quantity of air is supplied to and returned from the airlock. This is the preferred FDA airlock type when containment is not an issue.

The Pressure Bubble Airlock and the Pressure Sink Airlock have been used to separate biocontained clean areas from non-biocontained (either clean or non-clean) areas. In the Pressure Bubble Airlock, conditioned air from a clean, non-biocontained source is supplied to the airlock to pressurize it. The airlock supply air dissipates into adjacent areas through the airlock doors, walls and ceiling cracks or openings, thus preventing cross contamination between adjacent rooms and dirt from any adjacent areas from entering the airlock.

In the Pressure Sink Airlock, the airlock is maintained negative to all adjacent areas and all the air supplied to and infiltrated into the room is exhausted, thus preventing cross-contamination between adjacent areas. Of the two methods, the most commonly used and the one this author prefers is the Pressure Bubble Airlock since all particles or dirt are kept out of the airlock at all times. In the Pressure Bubble Airlock all particles or dirt are kept out of the airlock at all times. In the Pressure Sink Airlock particles and dirt from all adjacent rooms opening into the airlock are continuously passing into the airlock through door, wall, or ceiling cracks.

The Potent Compound Airlock is a combination of the pressure bubble airlock and the pressure sink airlock. A person entering clean rooms where potent compounds are handled needs to be fully gowned and, in most cases, use a respirator. This two-compartment airlock arrangement allows a person to protect (gown) himself before coming in contact with any dangerous material while at the same time, the product (potent compound) is protected from contamination from adjacent, connected areas. All conditioned, clean air supplied to the gown room is dissipated into the adjacent rooms while all the conditioned, clean air supplied to the

airlock room (as well as all infiltration air into that room) is exhausted.

Airlocks, Air Cleanliness Classification and Air Flow Rates

An airlock cleanliness classification and air flow rate (air changes per/hour) should match the cleaner of the rooms it serves, while keeping in mind the "cascading" principle. For example: a CL 10,000 room (using 60 AC/HR) should be protected by a CL 10,000 airlock having 60 AC/HR flow rate; a CL 100,000 room (using 20 AC/HR) should be protected by a class 100,000 airlock having a 20 AC/HR flow rate. An exception to this may be an airlock between a CL 10,000 room and a non-classified (95% ASHRAE) filtered area. In this case, the airlock should be classified as CL 100,000 (to maintain the "cascading" principle) but the airlock air flow rate should still be 60 AC/HR.

Another reason to maintain higher air flow rates in airlocks is to reduce time between airlock door openings and to prevent cross contamination between adjacent rooms when one of the doors of the airlock is opened. The airlock pressure rapidly approaches that of the opened room and contaminants can flow into the airlock. The second airlock door should not be opened until the airlock airflow has had a chance to flush the airlock. Typically, one room air change is used although some pharmaceutical companies prefer two air changes. This implies that for an airlock designed for 20 AC/HR, 3 minutes must pass before the second airlock door may be opened, however by using a 60 AC/HR the wait is reduced to only one minute. This time delay applies when passing from the dirtier room to the cleaner rooms. This long a delay is not needed when going from the cleaner room to the less clean one.

Some references that validate the above recommendations are:

- The European Commission GMP guide[1] paragraph 27 of Annex 1 states "changing rooms should be designed as airlocks…the final state of the changing room should, in the "at rest" state, be the same grade as the area into which it leads".

- The ISPE Baseline® Guide, Vol. 3 - Sterile Manufacturing Facilities[2] states under Sec. 5.7.1.1 for HVAC system design operational issues "…increase air changes to the busiest areas i.e. changing rooms"

- The 1999 ASHRAE Applications Handbook[3] Figure 8, page 15.6 shows a CL 10,000 Pressure Bubble Airlock protecting a class 10,000 biocontained suite.

General Materials of Construction and Direction of Door Swing

For an airlock to be effective, it's materials of construction and finishes are critical. Floors, walls and ceilings should resist chemicals used for cleaning and have non-flaking or shedding finishes. Walls are typically constructed of gypsum board on metal studs and finished with epoxy paint. PVC coatings or stainless steel finishes are also used. Ceilings should also be constructed of gypsum boards and finished with epoxy. Joints between walls and ceilings should be coved. Doors, windows and lights should be flush. Floors should have integral coved bases and be constructed of poured concrete with epoxy resin finish or epoxy terrazzo with granite aggregate. Floor sealers should resist chemicals used for cleaning the airlocks. Doors should have perimeter seals at frame and floor sweeps. Whenever possible, doors at airlocks should open to the dirtier or biocontained side.

Airlocks Pressurization

To find out the required pressure differential required between adjacent rooms of different cleanliness, both the USA and the European Community (EC) GMPs have to be examined. The USA Aseptic Processing Guide[4] requires a static pressure differential of 0.05 inches w.g. between adjacent areas of different air cleanliness classification for both "controlled and critical" areas; the EC Guide gives a range of 10 to 15 pascals (0.04 to 0.06 in. w.g.). Therefore, a differential of 0.05 in. w.g. satisfies both GMPs.

The next step is to decide where this differential applies in relation to the various types of airlocks shown in Figure 1. For the Cascading Pressure Airlocks the 0.05 in. w.g. differential should be between the clean room and the non-classified corridor. It is not between the clean room and the airlock or between the airlock and the corridor. In both, the Pressure Bubble and the Pressure Sink airlocks, the differential should be between the airlock and the corridor and between the airlock and the biocontained area. A second factor to be considered for these two airlocks is biocontainment requirement. The bioncontainment area should always be negative to any adjacent non-biocontained area; therefore, if both airlock doors are mistakenly opened simultaneously, any airflow should be from the non-biocontained to the biocontained area. For this reason, Figure 1 shows the biocontained area at a lower pressure than the adjacent, non-biocontained area, although the biocontained area is cleaner than the corridor. In Figure 1, it is seen that even if the three doors of the Potent Compound Airlocks are inadvertently left open, the airflow will still be from the non-biocontained area (the corridor) to the biocontained area.

Pressurization CFM Calculations

Once it is determined what the differential should be across the airlocks, a "guesstimate" has to be made of the pressurization CFM requirements. It is a "guesstimate" because until construction is finished, the actual CFM required can not be measured since it depends on the airlock "construction tightness" and door seals. For calculation, it is assumed a "tight construction" (gypsum board ceiling, door seals, and closed doors). Although there are various methods of calculating air leakage for rooms, the following method is the one this author prefers due to its simplicity and the "conservative" CFM values obtained. It has also been proven throughout many installations.

The CFM calculation method is the "door crack leakage" method. It is assumed that door perimeter and joints (if two leafs) have a 1/8" crack and that there is a 1/4" crack between the door and the floor. For sliding doors a 1/2" crack is assumed around the whole door perimeter. The CFM calculation formula used is CFM = CAV where "A" is the area of crack area in "square feet", "V" the velocity pressure in feet per minute (resulting from the conversion of static pressure to velocity pressure to move the air through the door cracks where V = 4005 $\sqrt{P}$ diff), and "C" is the pressurization loss coefficient for air movement across a linear crack. This value is typically between 0.60 and 0.80 but this author prefers to assume it as 1.0 for simplicity of calculations and to be "conservative" on the CFM values calculated.

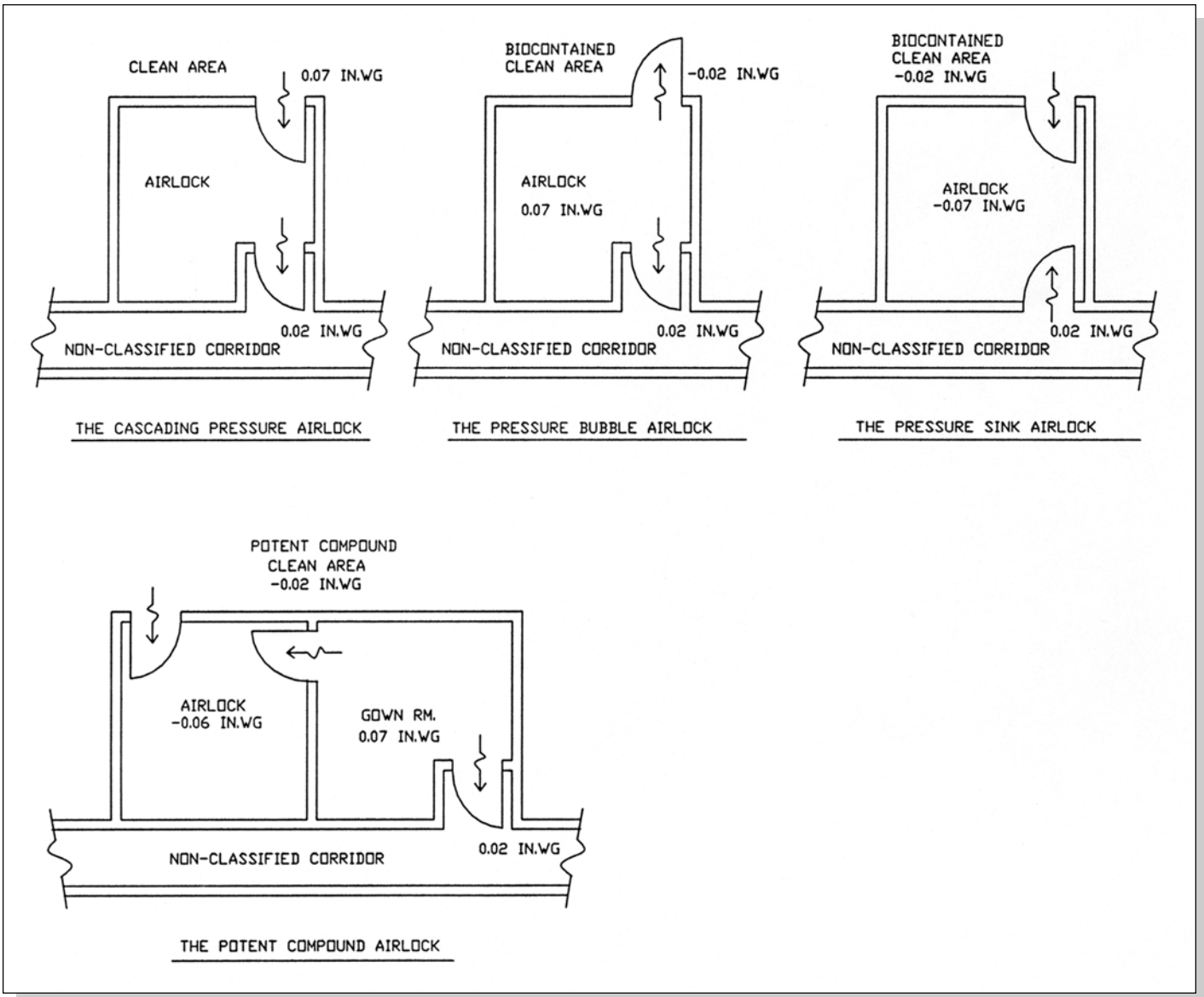

Figure 1. Types of airlocks.

Figure 2 shows the crack areas obtained for three typical door configurations as well as a tabulation of velocity pressure and velocity.

Assume in Figure 1 that all doors are 3' x 7', that each airlock is 8' x 10' x 9' high, and that the airlocks are class 100,000 with an air flow rate of 20 AC/HR . The required supply CFM becomes: CFM = Vol x ACHR/60 = (8' x 10' x 9') (20) / 60 = 240.

For the Cascading Pressure Airlock, to maintain pressure differential across the clean and the non-classified area assume one of the airlock doors is open. The pressurization CFM for a pressure differential of 0.05 w.g. is then: CFM = A x V or CFM = 0.24 sq. ft. x 896 FPM = 215 (say 210). With both airlock doors closed, the CFM leak between the clean room and the airlock is the same as between the airlock and the corridor; therefore, the return CFM of the airlock is the same as its supply CFM or 240.

For the Pressure Bubble Airlock, the pressurization CFM for each door is different. For the corridor door: CFM = A x V = 0.24 x 896 = 215, say 210 (for a pressure differential of 0.05 w.g.). For the clean room door: CFM = 0.24 x 1201 = 288, say 290 (for a pressure differential of 0.09 in. w.g.). The airlock minimum supply CFM is still 240 (see above) but to satisfy air pressurization it will have to be bumped up to 500 (210 cfm + 290 CFM). The exhaust CFM will be zero since it is assumed all supply air will be dissipated as pressurization CFM.

The Pressure Sink Airlock will also have different pressurization CFMs for each door. The corridor door pressurization CFM = 0.24 x 1201 = 288, say 290 (for a pressure differential of 0.09 in. w.g.), the biocontained room door pressurization CFM = 0.24 x 896 = 215, say 210 (for a pressure differential of 0.05 in. w.g.). The minimum supply CFM to the airlock is still 240 CFM but the exhaust CFM becomes 740 (290 + 210 + 240).

In the Potent Compound Airlock each door will have a different pressurization CFM requirement:

- Door between clean room and airlock: CFM = 0.24 x 801 = 192, say 190 (for 0.04" w.g. Pressure Diff.)
- Door between airlock and gown: CFM = 0.24 x 1444 = 347, say 350 (for 0.13" w.g. Pressure Diff.)

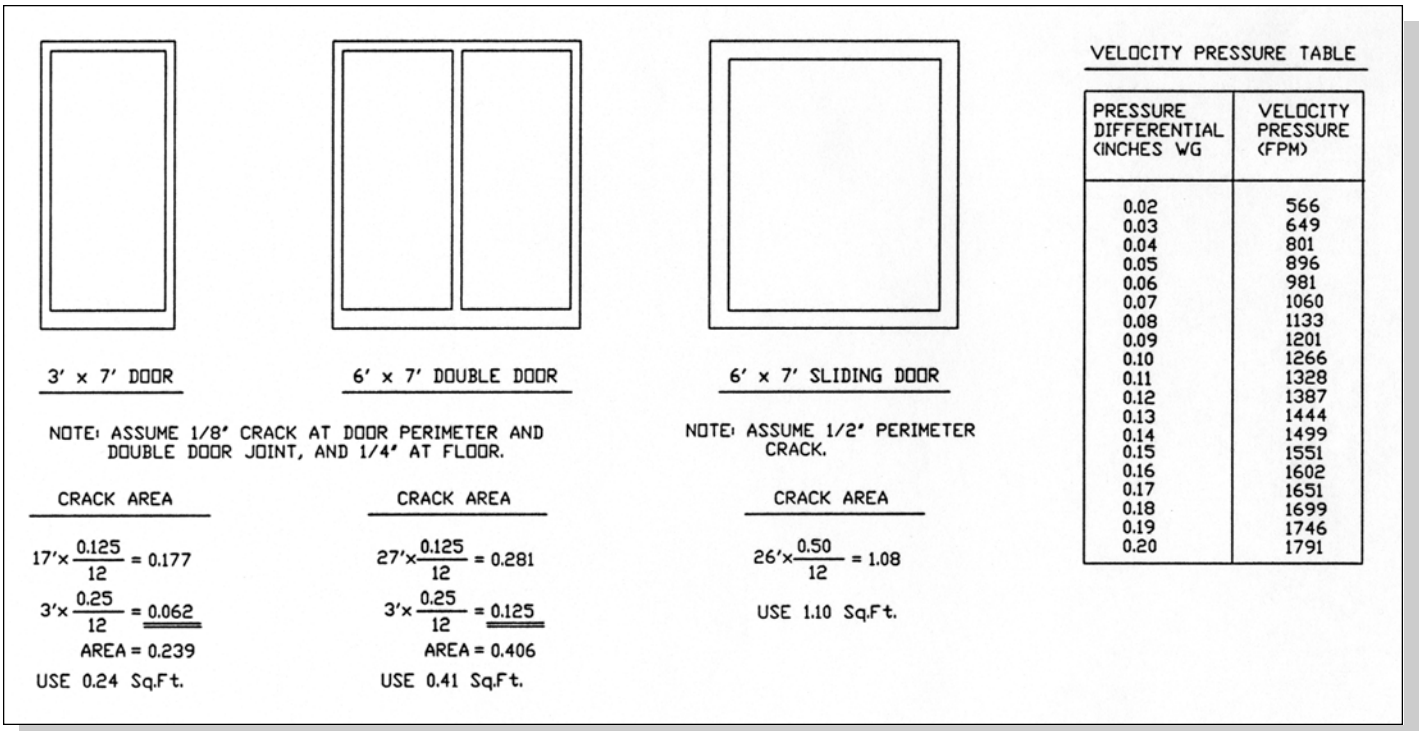

Figure 2. Crack area calculation and velocity pressure table.

- Door between gown and corridor: CFM = 0.24 x 896 = 215, say 210 (for 0.05" w.g. Pressure Diff.)

The minimum supply CFM to the airlock and the gown room will be 240 CFM each but the gown room will require 560 CFM (350 + 210) to satisfy pressurization requirements. The gown room return will be zero and the airlock exhaust 780 CFM (190 + 350 + 240).

Air Distribution for Airlocks

An important decision on airlocks is the source of conditioned air to be supplied to the airlocks. In the Cascading Pressure Airlock, supply air source could be the same duct branch serving the clean room the airlock is protecting. In multi-products, biocontained, or potent compound application, the source of conditioned air to the airlock/gown/degown rooms should be a clean, once through source. Typically, supply air is located at the ceiling using ceiling terminal HEPAs or non-induction type diffusers near the cleaner side of the airlock. The return/exhaust is typically located on a low wall, near the dirtier entrance to the airlock. Figure 3 shows air distribution schemes for the four types of airlocks shown in Figure 1.

Air Balancing of Airlocks

Procedures for air balancing of airlocks vary, depending on type of airlock. For the Cascading Pressure Airlock, the Pressure Sink Airlock, and the airlock room portion of the potent compound airlock, the supply air minimum CFM must satisfy the clean air classification air changes per hour. The return/exhaust CFMs are then adjusted to obtain the required pressure differential. This means that the pressurization and return/exhaust air quantities on construction drawings are just good "guesstimates" until the actual CFMs are determined at balancing time. For the Pressure Bubble Airlock and the gown room portion of the potent compound airlock the supply CFMs and the exhaust CFMs are temporarily set to the values shown in the construction drawings. If room pressure is high, the supply CFM is first reduced to obtain design pressurization (down to the minimum required to maintain the required air changes per hour). If pressurization is low, the return/exhaust CFMs are throttled to increase room pressure up to the design value.

A good example of the latter balancing method is the Pressure Bubble Airlock. The minimum supply CFM to maintain 20 AC/HR in this room is 240. The "guestimated" CFM to maintain pressurization is 500. If the room is tightly built it will be possible to reduce the supply CFM (down to a min. of 240) to obtain pressurization.

Temperature Control For Airlocks

Temperature control schemes on airlocks vary depending on type of airlock and source of conditioned air. Three schemes could include: no dedicated temperature control; dedicated control; and shared control with other adjacent airlocks/gown/pass-thru rooms.

A sample of "no dedicated temperature control" could be a system where the conditioned air source for the airlock is the supply air branch to the cleanroom with only the cleanroom having temperature control (typically controlling a reheat coil); the airlock room temperature is allowed to float. This means that most of the time the airlock is slightly colder than the room it protects. This typically is not a problem since personnel are in airlocks only a short time.

A sample of "dedicated temperature control" for an airlock could be a "pressure bubble" type airlock having multiple, double doors. Pressurization CFM will be so large that the room could get very cold. In this case, a reheat coil and thermostat is recommended, otherwise, the airlock will become too cold and humid.

A sample of "shared temperature control" is an application having a battery of gown-in/gown-out/pass-thru rooms located near each other, serving different suites. Since all these rooms

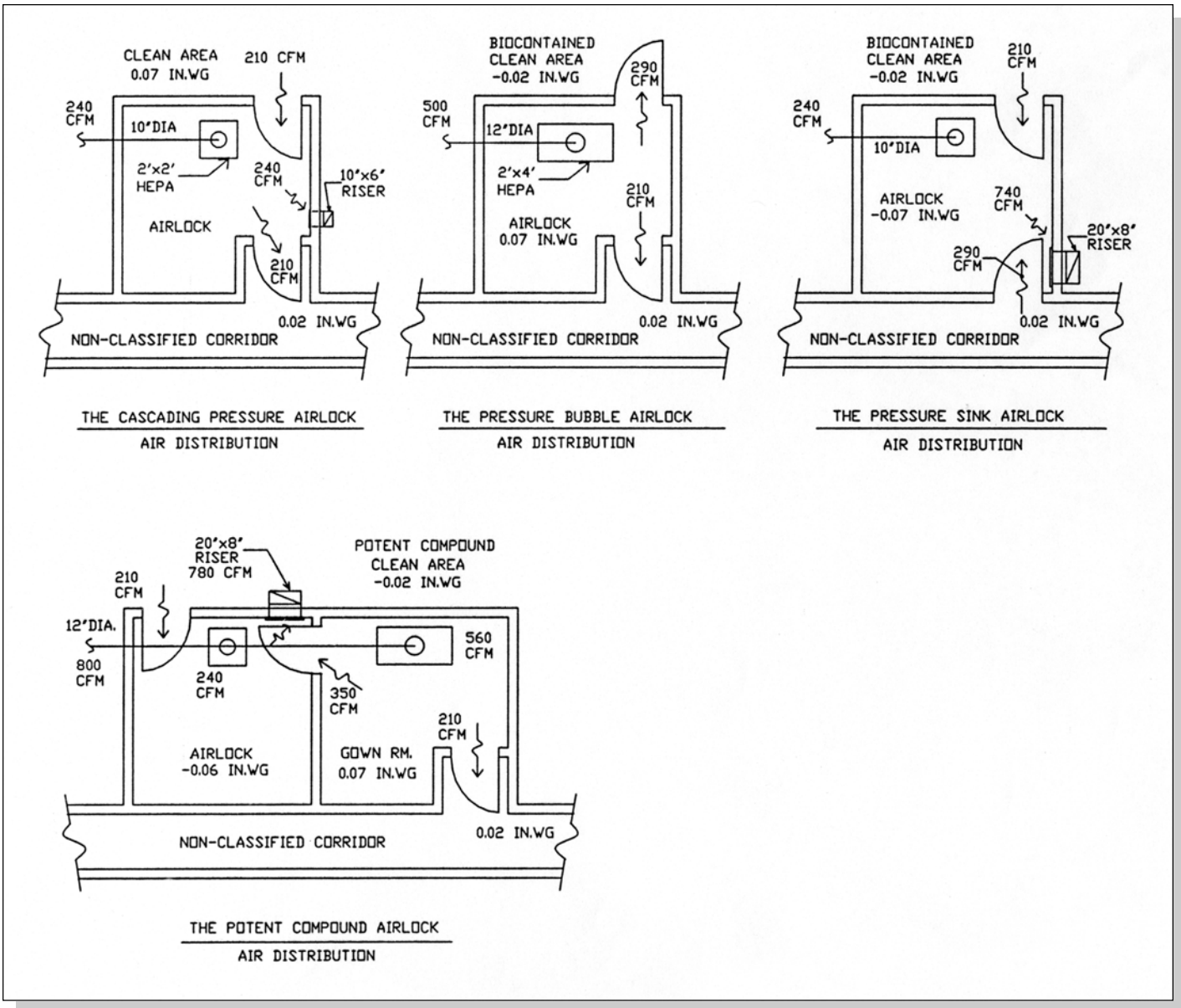

Figure 3. Airlocks' air distribution.

have similar and constant temperature and cooling/heating loads, one reheat and thermostat could serve all of them.

Pressurization Control For Airlocks

Before examining in detail some pressurization control schemes for airlocks, some general guidelines must be kept in mind. First of all, pressurization is to be maintained when all airlock doors are closed. Secondly, if two doors, or all doors are opened simultaneously by mistake, the direction of air flow from the cleaner to the less clean room must be proven, even though pressure differential cannot be maintained. Thirdly, the location of the static pressure probes is critical. For a cascade type airlock, the pressure probes should be located in each room the airlock is separating, not between each room and the airlock. For pressure bubble and pressure sink airlocks, pressure probes are required in all three rooms (each clean room plus the airlock). Fourthly, a common reference point should be used for all pressure differential readings. Typical locations include the plenum above the ceilings or a common interior corridor.

Lastly, a time delay is needed to allow for temporary door openings at airlocks before an audible and visual alarm is activated. The pressure differential range before alarms are activated could be set at plus or minus 0.02 inches WG.

Once the above general guidelines are followed, a decision has to be made whether to use static or dynamic pressure differential control. In static controls, pressurization is obtained during the test and balance (TAB) phase of the project. In this phase, balancing dampers are manually set and locked in position once pressurization is obtained. As follow-up, rebalancing may be done every six months when HEPA filters are checked or at least once a year.

Dynamic pressurization controls may be obtained in a number of ways. The simplest (and least costly) is manually setting the supply air damper to obtain design CFM and automatically controlling a motorized return/exhaust damper to maintain a specific pressure differential across the airlock. The more com-

plex (and more expensive) method is using constant volume boxes at the supply and return/exhaust ducts to the airlock, set to maintain a specific pressure differential across the airlock.

Conclusion

As can be seen from the above guidelines, application and proper functioning of airlocks is not a simple matter that can be taken lightly if airlocks are to be a barrier to cross-contamination. Good cooperation and coordination between the architect, the HVAC Engineer, the HVAC Controls Engineer and the Owner are a must.

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About the Author

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The article describes why managing for internal efficiencies in pharmaceutical companies is an attractive alternative to pursuing quick gains through mergers and acquisitions. It then proceeds to walk through a step-by-step process for doing so, and concludes by discussing two very relevant examples at different organizational levels of Eli Lilly & Co.

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Strategic Step-by-Step Approach for Managing Efficiency

by Scott Canute

"Efficiency-Ability to produce the desired effect with a minimum of effort, expense, or waste."[1]

Introduction

If there was ever a time where managing for efficiency was at the heart of business strategy for the pharmaceutical industry, this is it. It has almost become a cliché to talk about the pace of change in the industry. Global cost containment is putting unprecedented pressure on the industry's ability to recoup the huge costs to bring a single pharmaceutical product to market. In response to this dynamic and rapidly competitive environment, many pharmaceutical companies have sought to acquire and/or merge with other pharmaceutical companies. The list of deals done or speculation on those that may be done in the future is seemingly endless. One of the primary drivers for doing these deals is of course the thought that the combined companies will be more efficient than the individual companies on their own. However, the evidence is very strong that the vast majority of mergers are unsuccessful. In the pharmaceutical industry, the fastest growing companies continue to be those that stress internal growth.

There are of course other ways to manage for efficiencies besides mergers and acquisitions. The untapped potential within each pharmaceutical company remains enormous. While the industry has made significant improvement from the mindset of earlier days that costs weren't important as long as you had the right products, there is still a long way to go. Realizing this potential is not an easy thing to do. It is not glamorous. It is not a quick fix. Eli Lilly's Chairman of the Board, President and CEO Sidney Taurel sums up these points very well. "The bottom line is that from our perspective scale beyond the threshold of critical mass does not compensate for the disruptions associated with mergers and acquisitions. Again, the best bet is to develop and build both the critical mass and the implementation skills that can

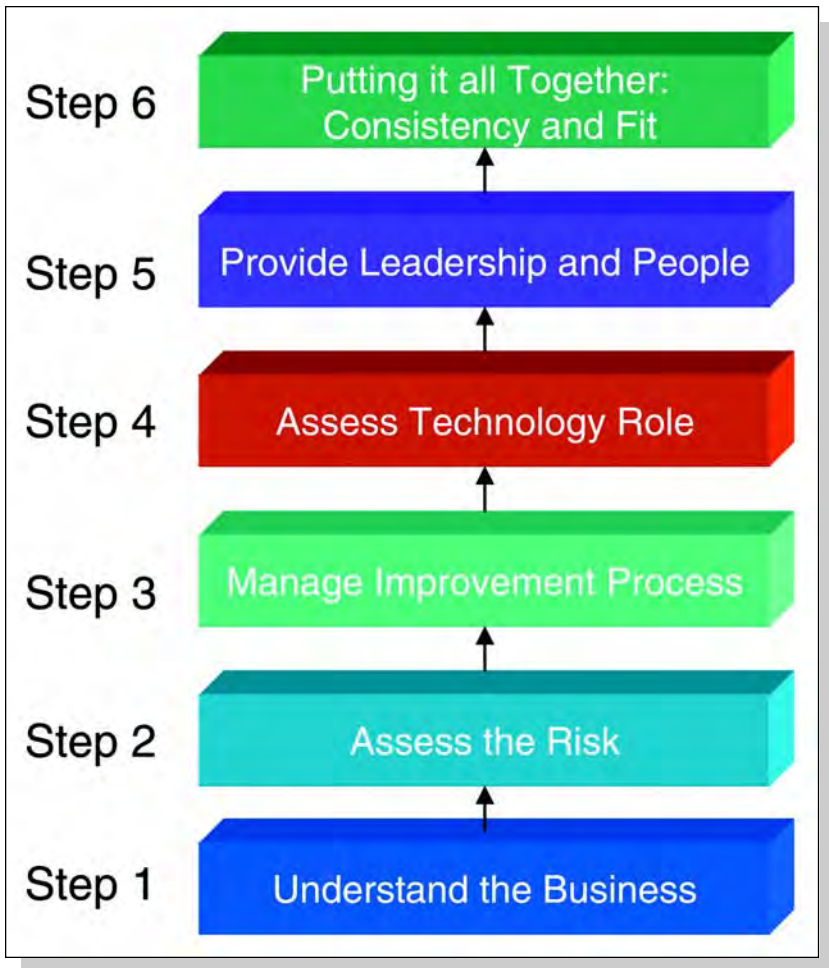

Figure 1. Steps for increasing efficiency.

consistently drive the "virtuous cycle" of investment and growth."[2] Realizing these internal efficiency gains is what the remainder of this article is all about.

There are several relatively simple steps that, if followed, can and will lead to significant efficiency gains - *Figure 1*. They are:

1. understand what capabilities your business strategy demands
2. make the appropriate risk assessment in terms of providing the needed capabilities
3. ensure that a robust management process is in place
4. assess the role technology can play
5. provide the necessary people and leadership
6. ensure that there is consistency and fit in all of the elements

There are many different models that could be equally effective in driving productivity, but this model works well at all levels in an organization. While the steps are simple to understand they are far from simple to implement. Far and away the most common failure is to look at only one or two of the elements in isolation of the others. More on that later.

Understand the Business

In order to understand your business better, managers must have a complete understanding of your company's or organization's business strategy. The key portion of the definition of efficiency that is stated above is "...to produce the desired effect…". All too often we focus too quickly on the other portion of the definition, that is "...minimum of effort or expense." Reducing costs is easy when you lose site of what capability you are trying to provide, be it supplying a product, developing a new process, or maintaining compliance. It is critical that you define what you are trying to accomplish and only then can you manage for efficiency. Cost reduction cannot be a business strategy by itself. This is particularly true in the pharmaceutical industry as we are dealing in many cases with life saving and highly profitable products. This doesn't mean that costs aren't important, but all businesses are built around providing a product and/or service. Don't ever lose sight of that fact.

Assess the Risk

Once the capability desired is defined, the key question then becomes how much risk is the business willing to take in terms of consistently being able to avail of that capability. The easiest way to illustrate this point is to put it in terms of a specific example - product supply. A conscious decision needs to be made about how much risk the business wants to take in terms of interruptions to product supply. When you first start asking these kinds of questions you are most likely to get answers like," I want 100% customer service levels and no interruptions." Zero risk must equal infinite cost by definition so choices must be made. Conversely, decisions could be made in the short term to increase plant utilization, which makes costs look good; however, the question arises as to whether the increase in plant utilization will increase the risk of not being able to supply product in the long term? Absolutely! The point is that increasing or decreasing risk is neither good nor bad, but the fact remains that the risk exists and therefore must be managed. While there are quantitative ways to measure risk, including the use of quantitative methods where possible, in most cases good judgment and intuition informed with data will be the most useful way of assessing risk. While this example is focused on product supply the logic is applicable to any capability that is desired from the business level all the way to individual processes on the shop floor.

It is important to remember that even within one company that we can participate in very different businesses with different economic profiles and therefore very different risk profiles. A consumer product is not the same as a new ethical pharmaceutical or a generic drug with many alternatives on the market. Many of the risk profiles of our businesses will change with product lifecycles so the risk profiles must be continually assessed. The fact that many of our products are life saving must be considered and will in most cases be the overriding consideration in terms of assessing risk if there are limited alternatives on the market.

Managing the Improvement Process

If an organization is going to truly manage for efficiency, it will need a very robust management process. Ideally, this will start at the top of an organization and will cascade throughout it; however, in the absence of a comprehensive organizational management process the major elements of the management process can be created anywhere and at any level in an organization. The critical pieces include:

- a full understanding of the business strategy and risk assessment on the problem or opportunity at hand
- translation of the elements of the strategy into metrics and targets
- some type of "gap analysis" that assesses the difference between the current state and the desired state
- creation of action plans to close the gaps
- a reporting or checking step that ensures that the action plans have the desired effect in the desired time frame or if not that the appropriate responses are taken
- a periodic review of the entire process to ensure that the business strategy has not changed significantly enough to warrant a change in metrics and subsequent gaps and action plans

These steps are shown graphically in Figure 2.

The translation of the business strategy into the appropriate metrics is the most important step in this process. If you can measure it, you have a much better chance of managing it. It is important that the metrics are comprehensive in nature and are made up of both leading and lagging indicators.[3]

Driving this continuous improvement philosophy is probably the most essential element of driving an organization toward efficiency. This is especially true in the pharmaceutical industry where change is difficult because of the regulatory environment in which we operate. We have a tendency to look for the big bang approach and try to minimize the number of changes we make; however, if we are going to truly realize the productivity that lies buried in all of our organizations, we need to be able to reach out and make improvement one step at a time. Or, as Mark Twain said, "Continuous improvement is better than delayed perfection."

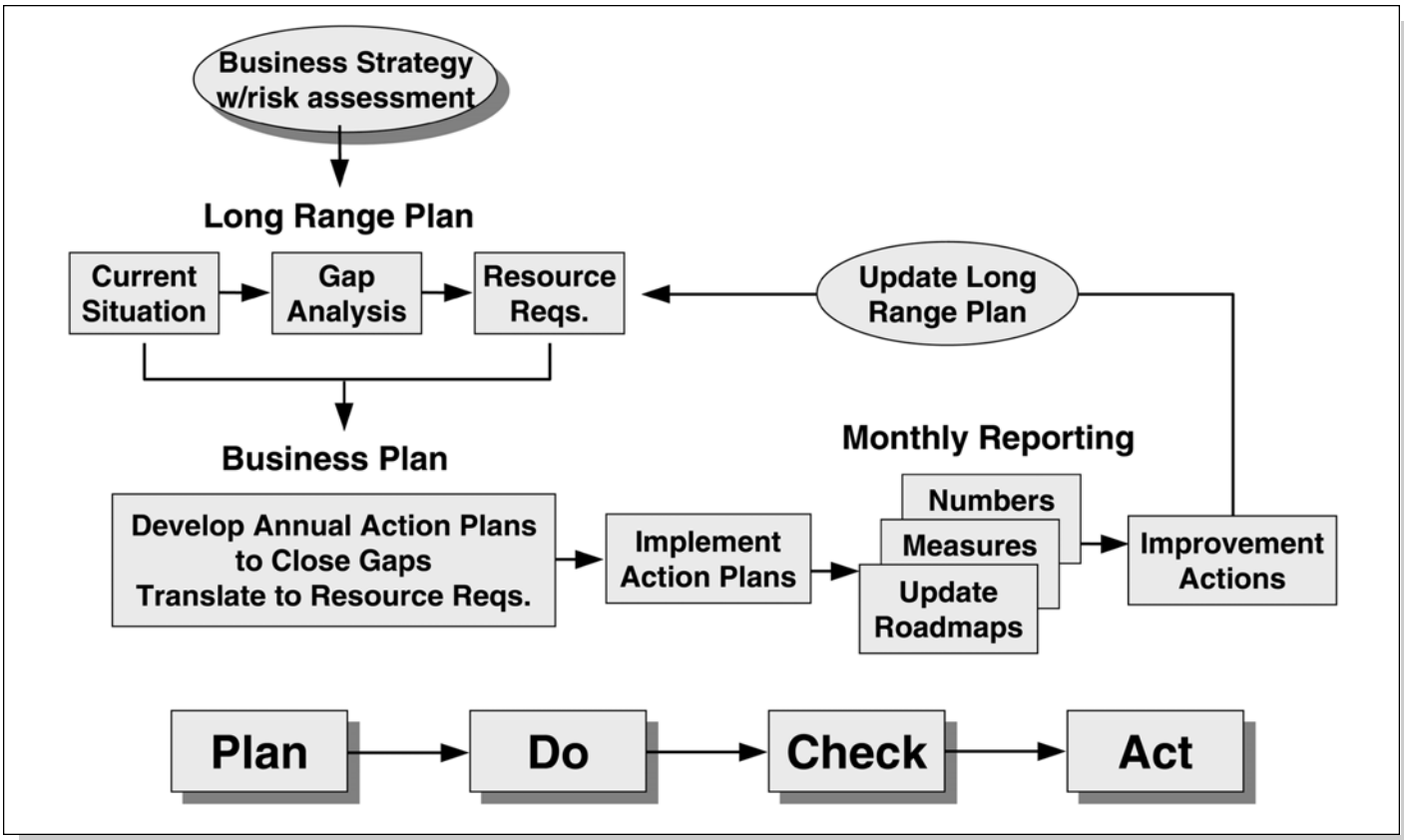

Figure 2. Manufacturing management process overview.

Assess the Role of Technology

Technology can be a key enabler of driving productivity improvements in the pharmaceutical business; however, it is critical that the role technology can play is properly assessed. Business is full of well intentioned technology improvements that have not achieved their original business objectives for a variety of reasons. One of the best-known examples is the $40 billion that General Motors invested in factory automation in the 1980s. As Ross Perot said directly to GM management at the time, they could have bought Nissan and Toyota outright for what they invested in factory automation while instead they watched their market share plummet from 46% to less than 35%.[4]

Does this mean that we should shy away from technology? Certainly not; however, when considering the use of technology, it is important to thoroughly assess a number of factors before proceeding. These factors fall into two general categories. The first is ensuring that your technology choices are connected with your business strategy and that it remains so for the life of the technology (or at least until a payback on the investments is obtained). The second is looking at **ALL** of the factors that make a new technology successful and ensuring that they are in a proper state of readiness. In most cases, implementing the new technology is the easiest part.

First of all, what specific gains are to be realized from the technology? Are there other alternatives to using the new technology? Is the business strategy likely to change in the near future making the technology no longer as relevant as it once was? What happens if the business does demand different things in the future? How easy is it to shift to new processes or are you stuck with the new technology for years to come? How fast is technology changing? Is something "bigger and better" coming soon? Are you better off to wait or move ahead? These are difficult questions to answer to everyone's satisfaction, but until you do so you would be advised to be very cautious about moving ahead with any technology projects.

Secondly, there are many elements that must be in place for a new technology to deliver on the projected benefits. The existing process where the technology will be used must be well understood and in sufficient control. We all have seen what happens when we automate an out of control process- we have an automated out-of –control process! A management process must be in place to ensure that the business benefits that the technology is to deliver are realized. This includes all the elements of a management process discussed above. Again, we have all seen examples where a new technology is being implemented and it becomes unclear as to why we are doing it; however, most importantly, it is critical to have the right leadership and people in place to realize the true benefits of the technology. With the right leadership, anything is possible. Without it, no technology will fill the gap. General Colin Powell shares an excellent anecdote in his autobiography:

"We were trying to figure out how much practice ammunition a tank crew had to fire to become proficient… We wanted to find out what combination of actual firing and the use of training devices produced the best performance. One tank battalion was given the maximum number of rounds. Another got fewer rounds. Another got fewer rounds still and more time on the simulator-trainers. The acid test was to take these differently prepared battalions out to the major qualification range, give them the same number of rounds, and see which did best. The answer turned out to be "none of the above." The battalions that did best were those with the best commanders. A good commander could motivate his men to excel under any conditions. "We're gonna win even if they give us one lousy round"

was the winning attitude. The new technologies were adopted, and they did make a difference. But we never lost sight of the reality that people, particularly gifted commanders, are what make units succeed."[5]

This leads directly to the next step- the importance of having the right leadership and people.

Leadership and People

It would be impossible to over emphasize the importance of having the right leadership and people in place to drive the most efficiency and improvement in any organization. As illustrated very nicely in the previous example from Colin Powell, good leadership can make up for a lot of other weaknesses in your management system. There have been volumes of material written about leadership so to try and do justice to it here would be impossible; however, in my own experience, I have found several critical qualities that must be present in an effective leader.

It all starts with character and integrity. These are the building blocks from which all good leaders (and people for that matter) are made. Integrity is a word that we use in a very casual way in today's society. Integrity is much more than "do we merely do what we say we are going to do." We must spend enough time thinking about the important things we are involved in, decide what to do, of course then do it, and explain to people why we are doing what we are.[6] This is the kind of integrity that you see in true leaders.

Effective leaders also have a strong sense of humility and are more than willing to listen to and involve others in what they do. They realize they don't have all the answers and aren't afraid of showing it. They will actively think out loud so as to come up with the best solutions.

They are not afraid to use their intuition and experience to set bold aggressive goals without having all the data, but are then more than willing to sincerely engage the entire organization in how to achieve the goals.

These are the kind of leaders that need to be at all levels in the organization if you are going to effectively manage for efficiency. These are the leaders that will instinctively know how to mobilize all of the people in an organization behind the needed efforts. They will create the right culture where a spirit of continuous improvement will flourish.

Consistency and Fit: Putting it all Together

Hopefully by now this last point has become obvious. Any one of the previous dimensions by itself is not sufficient to realize significant productivity improvements. All must be present and there must be consistency and fit between each element. Having great technology with great people is worthless if they aren't connected to the business strategy. Having the greatest technology in the world won't help you at all if the people aren't in place to realize the benefit of the technology. It is critical to have a robust management process in place to pull all of the elements together or they can become disconnected from each other over time. Assessing how much risk the business is willing to take is the starting point for driving all productivity efforts.

The best way to illustrate how these all fit together is to demonstrate their effectiveness through a couple of examples. While there are many that I could use, I will choose two that illustrate nicely how these steps can work both at a shop floor level around a very specific business problem as well as across an entire organization.

The first example involves our Irish plant in the mid-90s. In one of our bulk pharmaceutical production buildings, it was becoming clear that we were reaching full capacity utilization. Looking very closely at the business needs and our pipeline of new pharmaceutical products, it was clear that significant amounts of new capacity were going to be needed. Historically, we would have then gone about designing and building a new production facility costing tens of millions of dollars. However, in this instance John Flanagan, the production head at the site, took a different approach. Thoroughly assessing the risk of having too much capacity versus not having enough, John and his team decided that they could create the needed capacity by driving productivity improvements from within the production building. This was a very clear business objective that John mobilized his entire team around. He made a firm commitment to the corporation of the goals that were to be achieved in terms of capacity generation so the effort was very visible. He installed a very robust building management process that focused on achieving the primary objective while maintaining other important objectives such as quality and safety in control. He also used technology very effectively to achieve the goal in terms of process automation, process data historians, etc. John and his team were so effective that they were able to delay the need for a new production building entirely for five years saving the company significant amounts of money.

The other example is the vast cost improvement that our entire manufacturing organization has achieved over the last several years under the leadership of our Vice President for Manufacturing, Mike Eagle. In order to respond to the severe cost containment pressures that the pharmaceutical industry has been facing throughout the 1990s, the Eli Lilly manufacturing organization set a very aggressive goal of achieving a 25% reduction in unit costs and aligned the entire manufacturing organization around achieving this goal. Again, this was a very visible and understandable goal both within the manufacturing organization as well as outside of it and one clearly driven by urgent business needs. A strong management processes was put in place to deliver on this goal including a comprehensive set of metrics starting from the top of the organization that cascaded throughout it into each plant site. All 10,000 + employees had specific objectives in their performance plans that related to this goal. A supply chain management organization was created to ensure that we could look at each individual product and business across the entire supply chain and appropriately understand the business strategy and supply risk profile for all of our products. We ensured that we had a comprehensive Human Resource Planning process in place across all levels of the organization to ensure we had the right people and leadership to make the changes happen. We also put a technology management process in place that ensured we were managing our technology across the relevant technology platforms (small molecule active, parenteral, etc.). This effort was so successful that we were able to actually reduce our unit costs by 40%, well exceeding the 25% goal.

As you can see from these two examples, it is indeed possible to make significant efficiency gains within an organization by following the very simple steps outlined in this article. However, and I can't emphasize this point enough, just because it is simple does not make it easy. Managing for efficiency is very difficult because it must impact everything that you do in every way. Managing for efficiency is hard, grinding work that must be taken one step at a time. Because it is hard, it will probably always be very tempting to look for the easy way out such as mergers and acquisitions in this world of instant answers.

However, if the right focus, patience, and determination are there, great efficiencies can be gained within our organizations.

One final thought for those that may think business deals are the way to efficiency. Even after a merger or acquisition, the efficiencies must still be gained in the combined company. If we can't achieve the efficiencies that are right there in our own organizations in front of our eyes, how do we expect to do so in a new combined company where we don't know the culture or the people? Is it possible that one of the reasons that so many mergers and acquisitions have failed is just what we have been talking about? While there are many reasons for mergers and acquisitions and they will always be part of our environment we should all look more closely at what we can gain within our own organizations. Managing for efficiency may not sound glamorous, but it can be effective and I can assure you it is a lot more fun than the potential alternatives.

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About the Author

Scott A. Canute was promoted to Vice President, Manufacturing for Eli Lilly and Co. in February 2001. He will become a member of the senior management forum. Prior to this, Canute was vice president, Pharmaceutical Manufacturing and Strategy. He had been general manager of manufacturing for European operations since 1998. Born in Traverse City, Michigan, he received a BS in chemical engineering from the University of Michigan in 1982 and an MBA from the Harvard Business School in 1991. Canute joined Lilly in 1982 as a chemical engineer in the plant engineering group at Clinton Laboratories. He had various engineering positions at Clinton Labs and worked in technical services before becoming department head of product recovery operations in 1987. In 1989, he worked briefly in international treasury before taking a leave from Lilly to attend Harvard University. He returned to Lilly in 1991 as manager of manufacturing strategy development. In 1993, he became manager of human resource business planning before transferring in 1994 to serve as general manger of Eli Lilly S.A. (Irish Branch), where he was responsible for manufacturing facilities in Kinsale, Ireland. Canute is Secretary of the Pharmaceutical Research and Manufacturers of America (PhRMA) Manufacturing Steering Committee and a member of the advisory board of Tauber Manufacturing Institute, University of Michigan.

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