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A New Suite of Automated Bioreactors at Genentech: A Case Study Employing Standards, Guidelines, and Software: From Requirements to Validation

by Ronald E. Menéndez

This case study reports on one effort to design and automate a suite of bioreactors employing *ISA-S88.01, Batch Control, Part 1: Models and Terminology*[1] standard, *GAMP 4* guidance, and S88-based batch management software widely used in the manufacturing industry.

Introduction

In response to strong market demand, aggressive competition, and pressure from investors to accelerate the time to market for revenue-producing products, biotech and pharmaceutical companies are viewing manufacturing process automation as a key strategy to achieve operational efficiencies, regulatory compliance, profitability, and growth.

Process automation not only supports the tightly documented "state of control" that is required for FDA compliance; it also can be a valuable strategy for improving productivity, reducing product variance, and achieving flexible manufacturing objectives. With these increasing expectations, process automation projects are often stretched to the limits of budgetary, quality, and scheduling constraints. Fortunately, recent years have seen the emergence of standards, adoption of guidelines, and development of innovative software to support these automation efforts.

This case study reports on one effort to design and automate a suite of bioreactors employing *ISA-S88.01, Batch Control, Part 1: Models and Terminology*[1] standard, *GAMP 4* guidance, and S88-based batch management software widely used in the manufacturing industry. Highlighted are the benefits of leveraging these resources from requirements gathering to the end goal – a validated and regulatory compliant automated system.

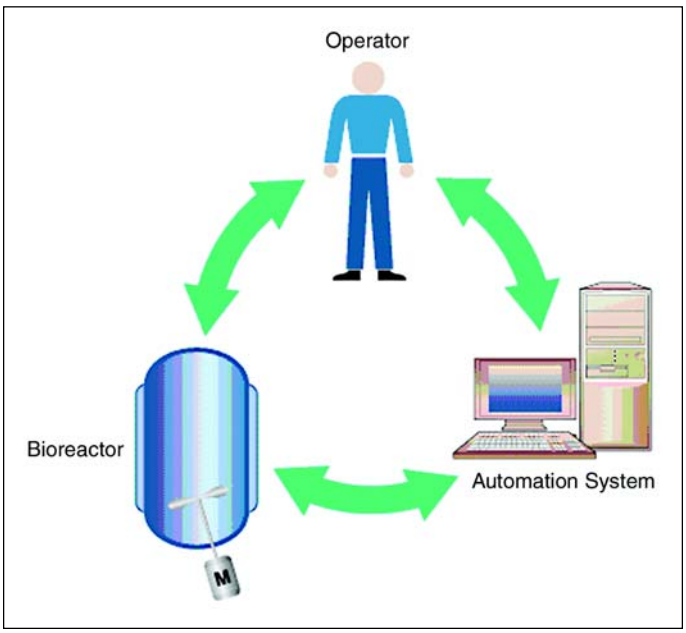

Figure 1. A multi-departmental, cross-functional team developed requirements for interactions between the operator, bioreactor, and an automation system.

Through this effort, Genentech realized substantial process management and productivity improvements and increased flexibility in the manufacturing area. The new automated system significantly reduced the overall production schedules and time involved in Clean-In-Place (CIP) operations. It also minimized operator interaction with the process, thus reducing the number of manual tasks and lessening the opportunity for errors.

Moving to Fully-Automated Production

One of the original products manufactured at the South San Francisco facility is a human growth

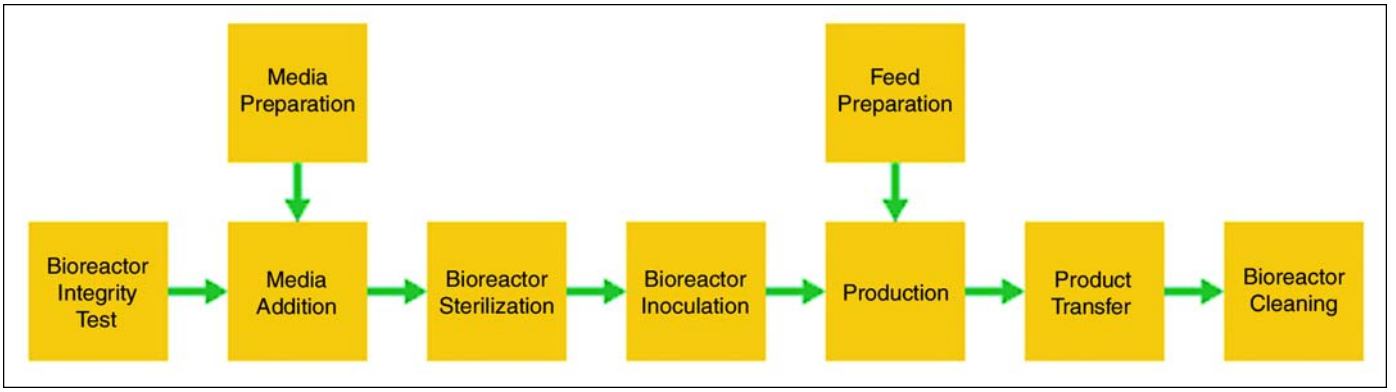

Figure 2. Simplified version of process flow for manufacturing of growth hormone in a production bioreactor.

hormone. In production for nearly 20 years, this product had been manufactured largely through semi-automated processes, supplemented in part by an older generation process control system. Production took place in a suite of bioreactors, ranging in capacity from 10 liters to 1000 liters.

Semi-automated processes had included Clean-In-Place (CIP), Sterilization-In-Place (SIP), and bioreactor operations. Media preparation and secondary feed preparation were performed in portable tanks. A pushbutton/switch panel with integrated single-loop controllers provided a modest level of process automation and supervisory control for bioreactor operations.

While effective for batch production, the operation was time-consuming and required extensive involvement by operators. It also did not enable the South San Francisco manufacturing operations to take advantage of new process automation advances and features. To address such concerns, Genentech decided to replace its technology with a state-of-the-art automation system. And recognizing that GAMP 4 was well on its way to becoming the standard approach for planning effective, regulatory compliant, and validated automated systems, Genentech elected to follow these guidelines.

GAMP Driven Planning

GAMP 4 recommends a process which initiates with the creation of Quality and Project Plans and a User Requirements Specification (URS). These steps are followed by the development of a Functional Specification that will meet user requirements and the Detail Design of the automation system that meets the specification. Following this method facilitates validation because each phase correlates directly with industry accepted procedures for Installation Qualification (IQ), Operation Qualification (OQ) and Performance Qualification (PQ), as depicted in the GAMP 4 V model.[2]

Genentech's Quality and Project Plans defined the procedures, standards, organizations, roles and responsibilities, processes, and documentation that would ensure a controlled and traceable development of the automation system.

To create the URS, Genentech assembled a multi-departmental, cross-functional team, and chartered it with the design, procurement, installation, start-up, and qualification of a suite of bioreactors and CIP equipment to revamp manufacture of their growth hormone product. The team included in-house engineering expertise in process design, manufacturing science, automation, and manufacturing operations, as well as applications engineers from the Distributed Controls System (DCS) vendor. The team defined the user requirements for interactions between the operator, bioreactor, and intended automation system, as depicted in Figure 1.

Through a series of well-documented meetings, team members analyzed the process flow and articulated their requirements for speed of operation, accuracy, quality, and efficiency in these interactions. It soon became clear to the team that a fully automated system would satisfy all requirements most effectively. Figure 2 shows a simplified version of the process flow at the production bioreactor class.

The decision was made to automate this manufacturing process completely, from media preparation and bioreactor integrity test, through media addition, bioreactor sterilization, bioreactor inoculation, feed preparation, production, product transfer, and bioreactor cleaning.

Equipping for Automation

Automating the manufacturing process raised the prospect that conducting many operations in parallel would shorten production time considerably. With this objective in mind, the team conceptualized equipment design and the S88 procedure control model in parallel.

The potential for parallel processing impacted the layout and design of the feed tanks, the production bioreactors, and the media tank, resulting in the suite of equipment partially depicted in Figure 3.

Transfer panels would be replaced by dedicated piping and valve manifolds which would eliminate the need for manual

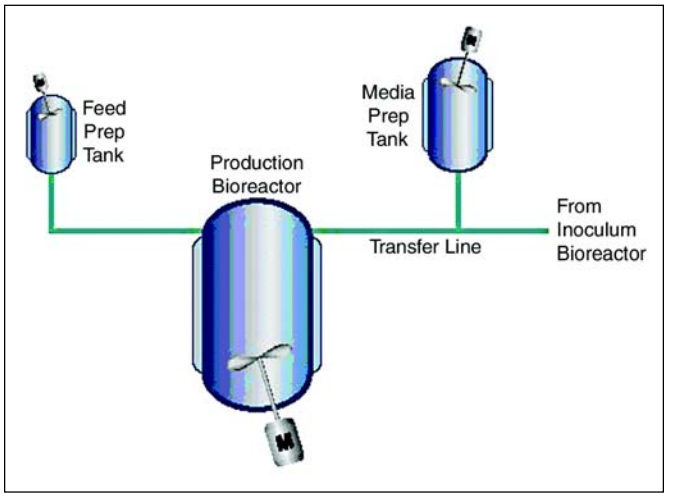

Figure 3. Generic equipment layout for a single production bioreactor.

jumper connections. The production bioreactors were hard-piped to the feed tanks on one end and to the transfer line from which the inoculum is transferred, on the other. The media transfer would be shared with the inoculum transfer line.

However, making this configuration work for parallel processing also required a system that would automate precise control of the cleaning, sterilization, and processing at each tank, using batch management software. The system would have to know when each step in the production process depicted in Figure 4 was completed successfully so that a new batch could be introduced into clean, synchronized equipment.

Recipe for Success

As parallel-processing efficiencies became increasingly feasible, however, it also became evident that the entire process could be integrated into a single procedure following the S88 standard.

A single procedure was built to operate the feed tank, the media tank, and production bioreactor shown in Figure 3, as well as CIP equipment which is not shown. Unit procedures were developed for each piece of equipment and then integrated into an overall procedure controlling the entire production cycle shown in Figure 4.

Through the batch management software an operator schedules and starts the procedure, known as the master recipe, the system creates the control recipe (a working version of the master recipe), acquires all equipment, sterilizes the equipment, places the equipment in production, and monitors the equipment through completion. As each unit procedure completes within the overall procedure, the transfer lines, tanks, and bioreactors are cleaned and ready for the next production cycle. Each procedure begins with clean equipment and leaves it that way, ready for the next use, as previously shown in Figure 4.

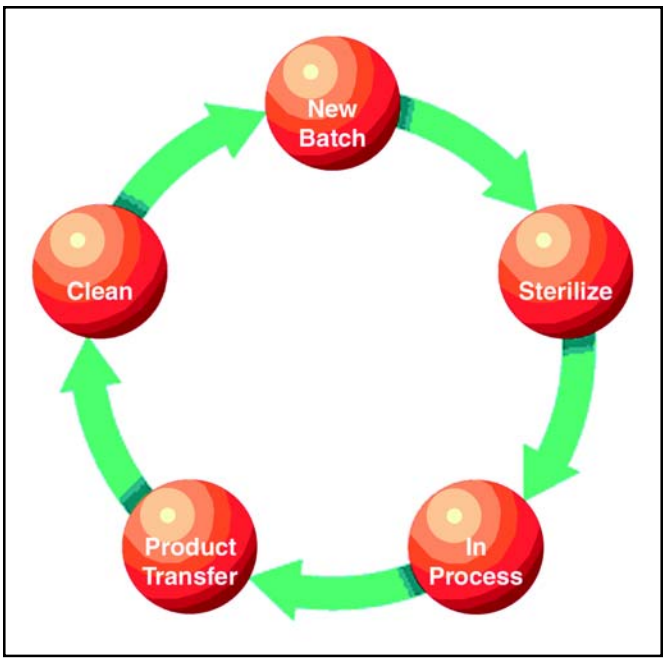

Figure 4. Cleaning, sterilization, processing, and product transfer were synchronized for each produciton cycle.

Figures 5, 6, and 7 depict the initial steps of the process

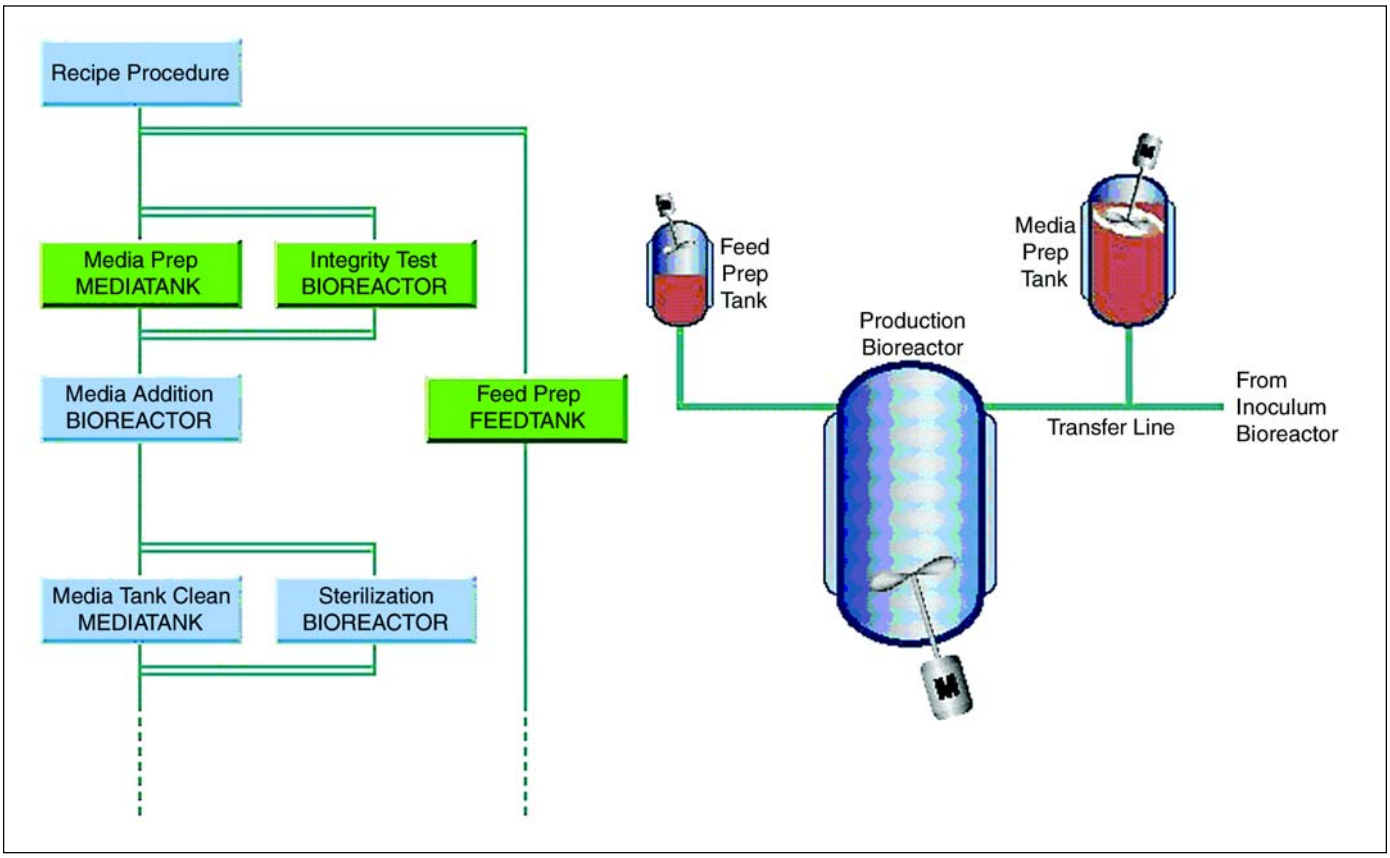

Figure 5. Bioreactor pressure test, media preparation, and feed preparation operate in parallel. (green indicates "In Process")

flow at the production bioreactor class. The figures show simple snapshots of parallel unit procedures during the first steps of the process shown in Figure 2 - media preparation, bioreactor integrity test, and media addition—up to the bioreactor sterilization operation only. However, these simplified snapshots do demonstrate the way in which the parallel processing and a single procedure combine to provide efficiencies throughout the entire process. When the procedure begins, the media preparation, bioreactor integrity test, and feed preparation unit procedures start simultaneously - *Figure 5*.

The media preparation and integrity test are then complete and media is added to the bioreactor, which goes in process. Feed preparation is still in process, for later transfer to the bioreactor, during production - *Figure 6*.

After the media has been transferred to the bioreactor, the media tank goes into the cleaning mode and the sterilization of the bioreactor begins simultaneously. The feed preparation tank remains in process for later use.

If coordinating these activities with multiple procedures, an operator would, for example, have to coordinate individual procedures for preparing and transferring media, others for sterilization, and still others for cleaning.

Automating these activities under control of a single procedure provides great efficiencies when compounded throughout the multiple steps remaining in the process flow of Figure 2. Key to the efficiency is synchronized repetition of the production cycle depicted in Figure 4. The fact that each vessel ends with a cleaning operation and is ready immediately for a new procedure, enables continuous processing and operation, which the plant performs with minimal manual intervention, 24 hours a day. The semi-automated CIP process of the bioreactor had previously taken two operators up to six hours to complete. Now, one operator can start the procedure, turn attention to another task, and return to a clean vessel, three hours later. In addition to expediting the process and improving productivity, the automated operation reduces the possibility of potential problems from human error.

Technology Infrastructure

Achieving this level of automation required replacing all original equipment. The efficiency gained with automation enabled reduction in the number of bioreactors while still delivering time-effective production improvement.

The DCS was used to automate the facility and was supplied with an ISA S88-based batch management software package that executes procedures, manages equipment, and collects batch production data. Delivered as a complete, PC-based platform including networks, controllers, I/O, communications, and operator interface workstations, the control system enables the open integration of applications as well as data, providing fault-tolerant control processors, redundant batch managers, and a highly secure, deterministic software architecture that is very well-suited for the application.

The control system workstations in the manufacturing

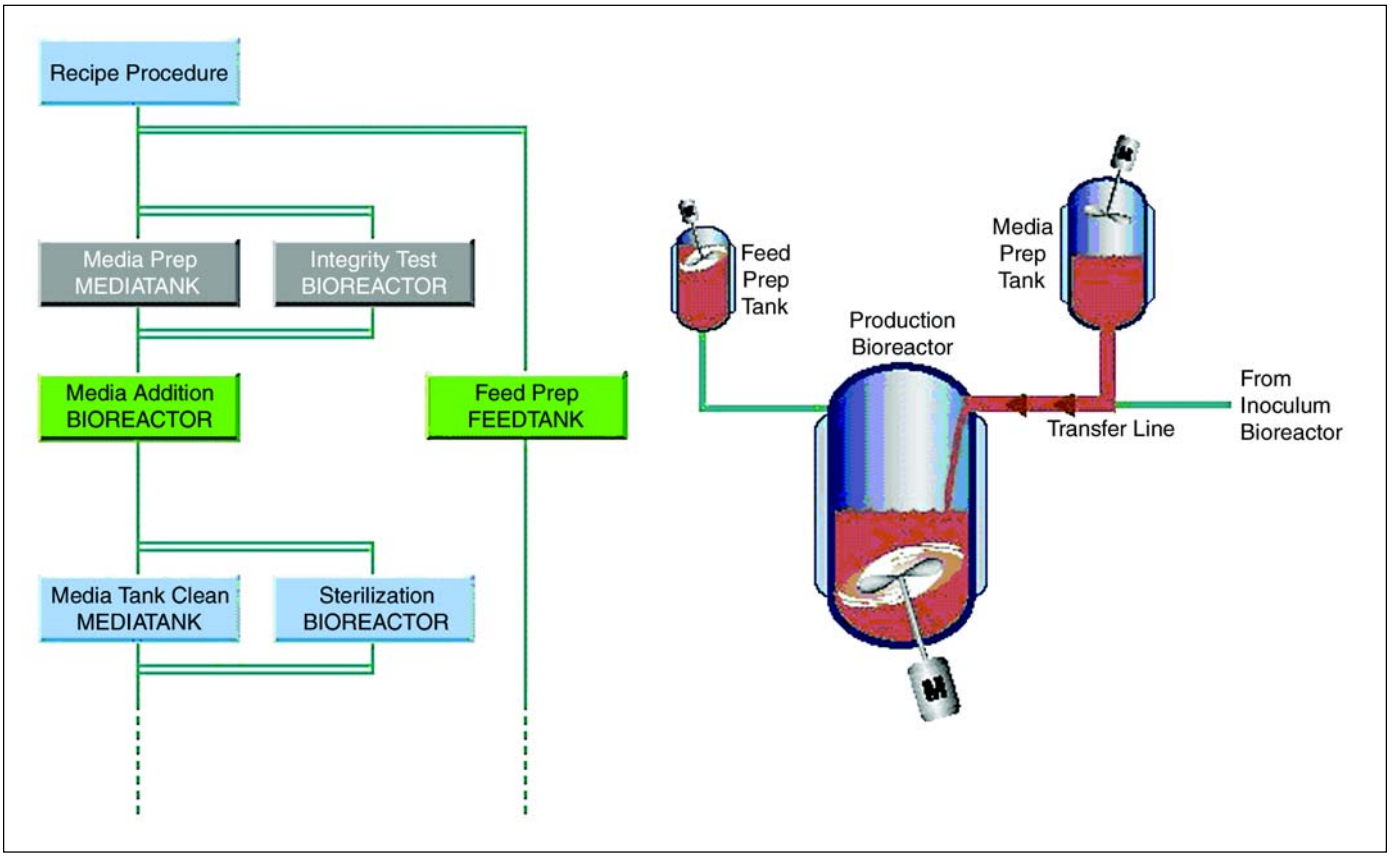

Figure 6. The bioreactor pressure test and media preparation complete in parallel, while bioreactor media addition and feed preparation process in parallel (green = in process, gray = completed).

area run Human Machine Interface (HMI) display graphics that help operators visualize and manage multiple procedures, equipment status, and production information.

The Bottom Line: Greater Efficiency and Easier Compliance

While Genentech's planning has always involved procedures for gathering user requirements, defining functional specifications, and designing the system around them, it was sometimes a varied and isolated process. GAMP 4 provided a consistent planning framework, which all members of the multi-departmental, cross-functional planning team respected. This structured, systematic attention to clearly articulate user requirements resulted in the following benefits:

- ***improved productivity, including reductions in process time and potential batch discrepancies,*** due to streamlining manufacturing operations, which enabled operators to schedule and execute a single, large procedure rather than manage many small procedures
- ***streamlined validation effort,*** by mapping IQ, OQ, and PQ activities directly to the User Requirements Specifications, Functional Specification, and Detail Design
- ***well-positioned for successful FDA inspection and audits*** by implementing GAMP 4 guidelines, which are becoming widely accepted as an industry standard

Genentech Background

Founded in 1976, Genentech's stated mission is leadership in the discovery, development, manufacture, and commercialization of bio-therapeutic products that meet significant, previously unmet medical needs. The company processes approximately three million liters of product annually through a variety of proprietary processes. Genentech's South San Francisco facility is the company's original manufacturing site, with its first processes licensed by the U.S. Food and Drug Administration (FDA) in 1985.

The South San Francisco facility includes multiple production and purification equipment and Clean-In-Place (CIP) systems, which have been revamped and upgraded over the years. Total production capacity exceeds 100,000 liters.

In addition to South San Francisco, the company operates a 420,000-square foot facility in Vacaville, California and a manufacturing facility in Porriño, Spain.

Such benefits will not be limited to human growth hormone production at the South San Francisco facility. The process also has resulted in templates and procedures which are being applied to other products and other Genentech facilities. Genentech is, for example, already applying the processes developed for the automated system to the production of a new bio-therapeutic anitbody, ranibizumab, which is now undergoing clinical trials. When it completes clinical trials,

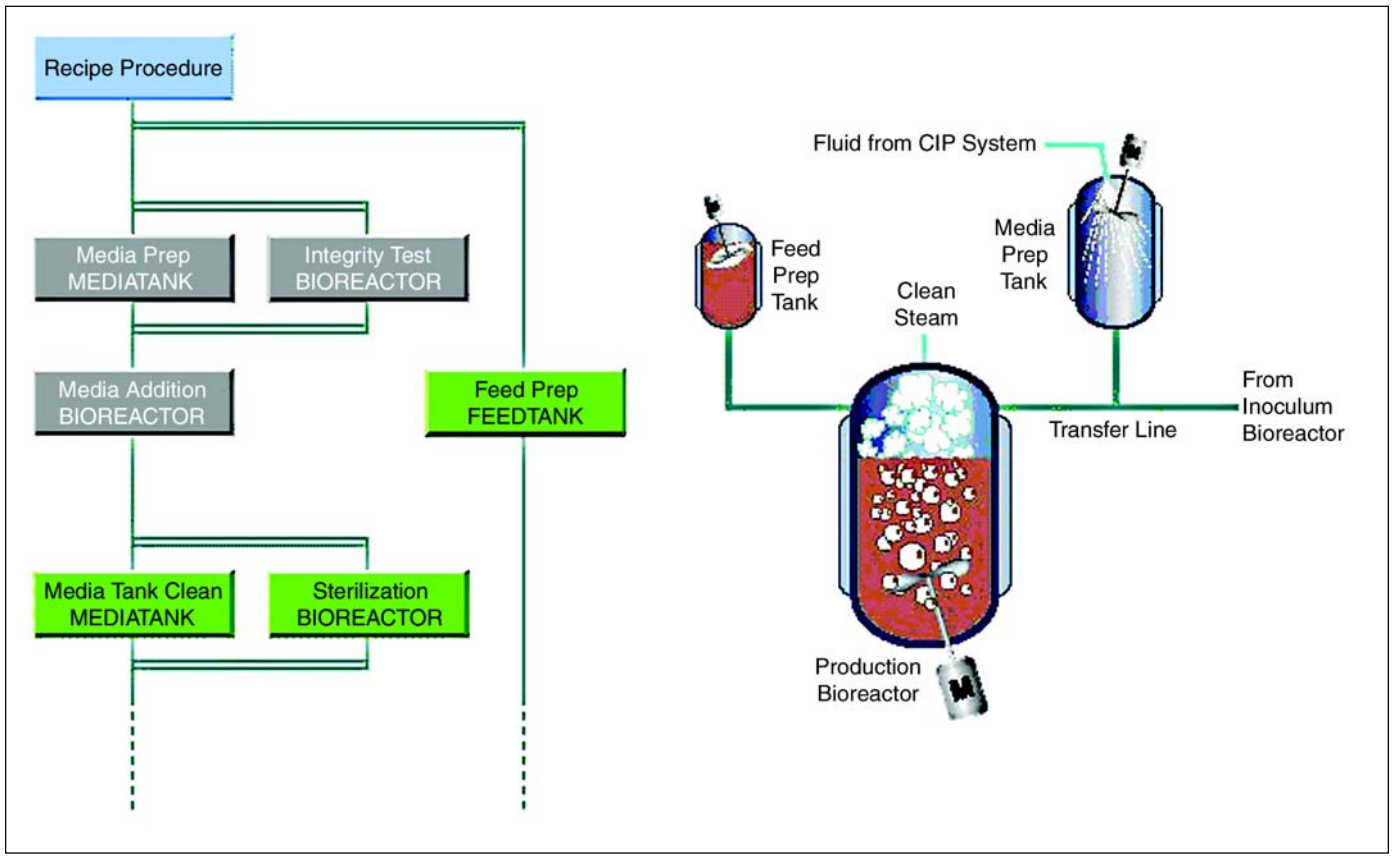

Figure 7. In process step three, bioreactor media addition completes, while media tank cleaning, bioreactor sterilization, and feed tank preparation process in parallel.

Genentech expects the new bio-therapeutic to be one of the first biopharmaceutical products to treat a form of Age-related Macular Degeneration (AMD), one of the leading causes of blindness in people over 60. In ways such as this, process automation is playing an increasingly important role helping Genentech fulfill its mission of addressing previously unmet medical needs.

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About the Author

Ronald E. Menéndez has more than 13 years of automation experience within the biopharmaceutical, pharmaceutical, chemicals, and consumer goods industries, and is experienced in a variety of control system platforms and batch management software. He is a Senior Automation Engineer in the Corporate Engineering Department at Genentech's headquarters in South San Francisco, where he currently serves as the lead design engineer for the automation of cell culture operations for its new facility in Vacaville, CA. Previously, he worked for the Sequencia Corporation, where he contributed to the development of S88 batch management software in the early 1990s; performed system integration and plant start-ups in Latin America, Southeast Asia, and Europe; and provided S88 consulting to biopharmaceutical and pharmaceutical companies. He holds a BS in chemical engineering from the Department of Chemical and Nuclear Engineering at the University of California, Santa Barbara. He can be contacted by telephone: 1-650/225-6397 or by e-mail: menendez@gene.com.

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This article describes an automated packaging line for pre-filled syringes. It discusses the process from inserting syringes into lead containers for shipping to loading the containers onto shipping trays.

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Case Study: Robot-Based Inspection and Packaging System for Radiopharmaceuticals

by James E. Akers, PhD, Yoshifumi Yabuuchi, and Kenji Yoneda

Introduction

Pharmaceutical manufacturing systems must comply with current Good Manufacturing Practices (cGMPs)[1] and therefore must provide consistently high product quality and extremely reliable operation. Radiopharmaceutical manufacturing requirements are rather unique because of both human exposure requirements and the short useful lifetime of many such products. Some other pharmaceuticals, such as antibiotics and anticancer drugs, also require specifically designed manufacturing systems and procedures to minimize the likelihood of personnel exposure to products which might be highly allergenic or toxic. However, radiopharmaceutical manufacturing systems present a further challenge since the risks include not only exposure to the formulated product, but also the need to control radiation emitted by the radioisotope. Therefore, the production system must be equipped with shielding capable of blocking gamma-ray emissions, which will readily penetrate the typical thickness of stainless steel plate used in the manufacture of standard process equipment, to minimize the likelihood of personnel exposure to radiation.[2]

Radiopharmaceuticals have a short useful lifespan due to the physical half-life of the radioactive isotopes used in these products. For instance, the lifetime of 99m Tc radiopharmaceuticals is 30 hours after manufacturing. Therefore, production tends to be irregular since manufacturers accept orders and prepare the products even on the day before the drug is used at hospitals. There are obvious benefits to systems that are extremely reliable allowing rapid quality release of product. Therefore, online process control and realtime inspection are highly advantageous to manufacturers of radiopharmaceuticals.

The new technology described in this article has been designed with the special requirements of radiopharmaceutical manufacturing in mind. This manufacturing system employs a robot-based inspection and packaging system for radiopharmaceuticals, which also could be applied to the handling of other products that are challenging in terms of human safety including, high pharmaceutical activity drugs, biologicals requiring special handling precautions, or products containing live microorganisms. Figure 1 illustrates the image of syringe line (left) and vial line (right). The system described in this article is an automated packaging line for pre-filled syringes

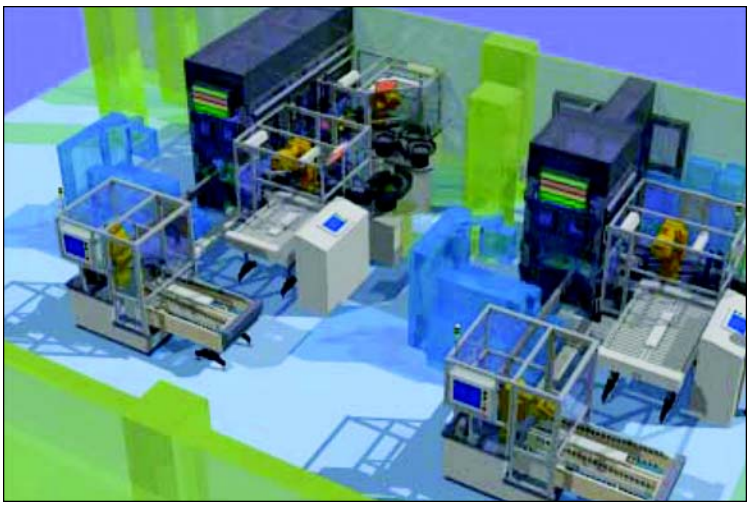

Figure 1. Image of lines.

Figure 2. Parts for pre-filled syringe packaging.

from inserting syringes into lead containers for shipping to loading the containers onto shipping trays.

Overview of the Syringe Packaging Line

- Materials to be handled: pre-filled syringes of radiopharmaceuticals and shielding packaging parts
- Scope of manufacturing operations: receiving pre-filled syringes, assembling, and inserting each of them into a product container, labeling, and loading the containers into a shipping tray
- Dimensions: about 6,500 mm (length) x 5,000 mm (maximum width)
- Capacity: 150 units/hour

Figure 2 shows all of the parts used for packaging a pre-filled syringe.

The side and bottom faces and top cover of the exterior package are made of lead to shield radiation during the transportation of the products to their point of use. The plastic lid is double-capped and encloses the product insert. The syringe body is in a tungsten shielded secondary packaging container to minimize radiation exposure during drug handling and administration. The product contained within the syringe can be visually checked by users through a viewfinder made of transparent leaded glass, which is made of approximately 70 percent lead oxide.

Figure 3 shows a packaging line for pre-filled syringes. In the lead shielding structure located far back in the middle of Figure 3, each pre-filled syringe is inserted into the tungsten-shielded container, and then packaged into the final lead container with cover to prevent radioactive emissions into the surrounding environment. Only the operations that pose a radiation risk are conducted with a lead shielded environment. Preparation of packaging components, for example, does not require any special radiation safety precautions and can be done in a typical transparent cabinet.

Design Concept

The system was designed to provide the following features, which were deemed critical in the production of radiopharmaceuticals:

1. reliable and stable operation
2. compact overall dimensions to minimize the amount of lead shielding required
3. fully automatic transfer of materials
4. fully automatic correction and/or rejection of non-conforming product
5. advanced production management system

A detailed description of each of these features is given below.

Reliable and Stable Operation

The achievement of stable and consistent operations can be difficult with conventional machines that rely on chain conveyors and turret with many grippers, even when they are designed and operated with great care.

The machine related problem is the grippers' dimensional deviation from allowable tolerance. This deviation can cause system aborts even when components are technically within their established dimensional specifications. The tolerances must be considered to design the equipment, including conveying equipment and grippers, to allow it to work adequately with components having the normal range of dimensional deviation. Therefore, conventional machines with many

Figure 3. Pre-filled syringe packaging line.

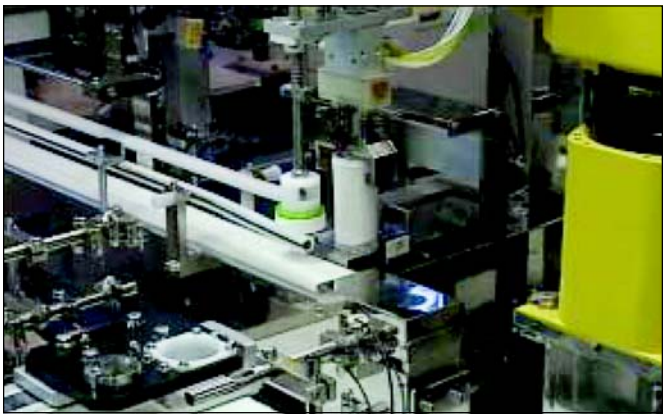

Figure 4. Multiple operation.

grippers and component transfer positions require exhaustive adjustment of the tolerance and frequent tuning of the equipment using carefully prepared production standards. Unfortunately, static measurements taken on components may not fully predict the "mechanical compatibility" of these materials under actual production conditions. Therefore, line stoppages, production aborts, and rejections may occur even when components are technically within their established dimensional specifications.

The components related problem is the changes to their properties after they are manufactured even if they are manufactured complying with all established specifications. Factors which can cause production changes in component properties include production lot, temperature, humidity, transportation, handling, and length of storage. Theoretically, careful attention to detail in quality control and production management can keep variability within the tolerance of the process equipment, but in reality, it is difficult to ensure that all components are within specifications at all times. This has been one of the major causes of machine aborts.

Therefore, we have found that conventional production facilities were less stable in operation and required more line stoppages for adjustment than the robotic system described in this article.

The robotic system minimizes the number of grippers required and compensates dimensional variation on materials or environmental effects by using properly designed and operated robots and vision systems. Thus, the use of robotics eliminates the need for frequent adjustment and diminishes the need for very tight component specifications. Figure 4 shows a robot transferring lead containers and top caps. Robots also can perform multiple functions such as transferring lead covers and syringes, for example, the same robot shown in Figure 4 also is equipped to perform inspection using vision systems.

The critical components are inspected through image processing to sort acceptable from defective or out-of-specification materials. Also, the system is capable of automatically verifying assembly status after the completion of each processing step. Figure 5 illustrates the detection of the presence

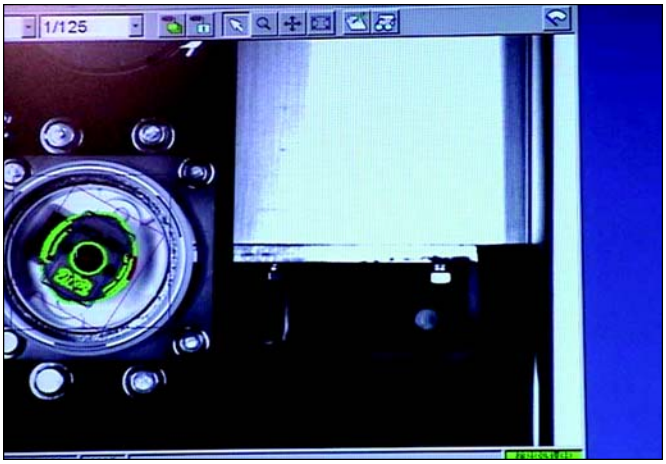

Figure 5. Vision check.

of syringes inserted into containers using video image analysis in conjunction with robot operation. The robot transfers only good products on an elective basis and automatically rejects any defective products by removing them from the production line. Such an operation in conjunction with robotic movement and inspection results in more efficient and safe operation with fewer line stoppages.

Additionally, this system enables the equipment to run consistently and efficiently with minimal operator intervention, factors that are extremely important for both quality product and operator safety considerations.

Compact Overall Dimensions to Minimize the Amount of Lead Shielding Required

The exterior package of radiopharmaceuticals consists of lead containers and covers to prevent radioactive emissions into the surrounding environment. The manufacturing system also must be equipped with lead shielding that covers the production line so that personnel are protected from exposure before the product is placed in its lead shielded final package. The thickness required for lead shielding is determined according to the energy of the gamma radiation emitted by the product. However, the amount of lead required to do this job can be minimized by downsizing or miniaturization of the processing line.

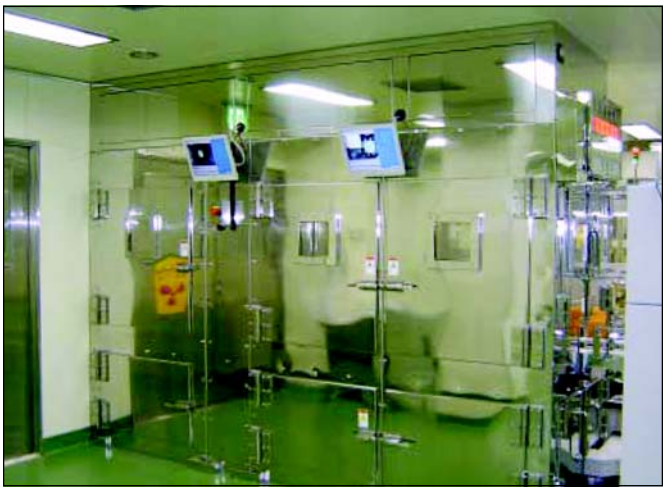

Figure 6. Lead shielding.

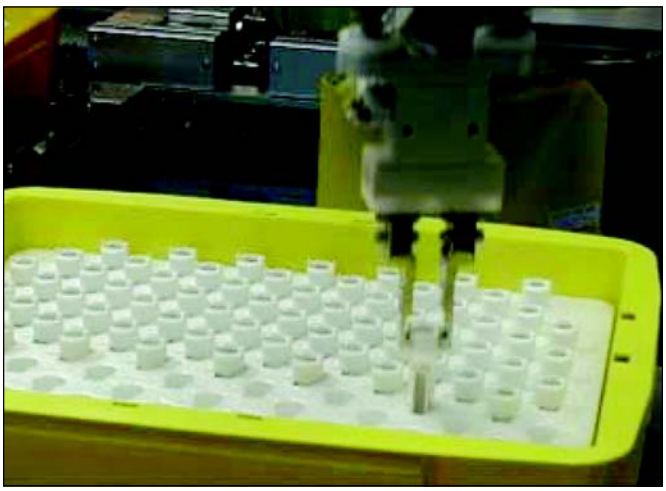

Figure 7. Tungsten-Shield containers.

Figure 8. Lead containers.

Machines that rely on conventional chain conveyors and turret with grippers tend to be large and require considerable floor space, and as a result need a comparatively large amount of lead shielding. However, the production system we are describing has been made significantly smaller than conventional automatic assembly equipment by assigning robots to handle multiple tasks such as component supply and handling operations. Thus, taking advantage of the versatility of robots results in a more economical use of floor space and the resulting miniaturization allows for a far more efficient use of lead shielding material. Figure 6 shows the lead shielding of a radiopharmaceutical syringe line. The syringe product shown consists of six different parts, and only two robots are required for all process operations up to the insertion of the syringe into its lead shielded final package within the lead shielding - *Figure 6.*

Fully Automatic Transfer of Materials

The lead containers and cover, and tungsten-shielded containers are returned to the factory in commercially available trays for reuse. With conventional systems, these reusable components must be manually transferred into a special carrier custom-designed to be compatible with the machines. These reusable components also must be visually inspected. In conventional systems, a custom carrier of some kind must be built with very high precision so that it can function properly with the equipment. Storage and handling of the custom carriers also requires special care.

The use of robotics enables the necessary exterior inspection and automatic supply of components by checking reus-

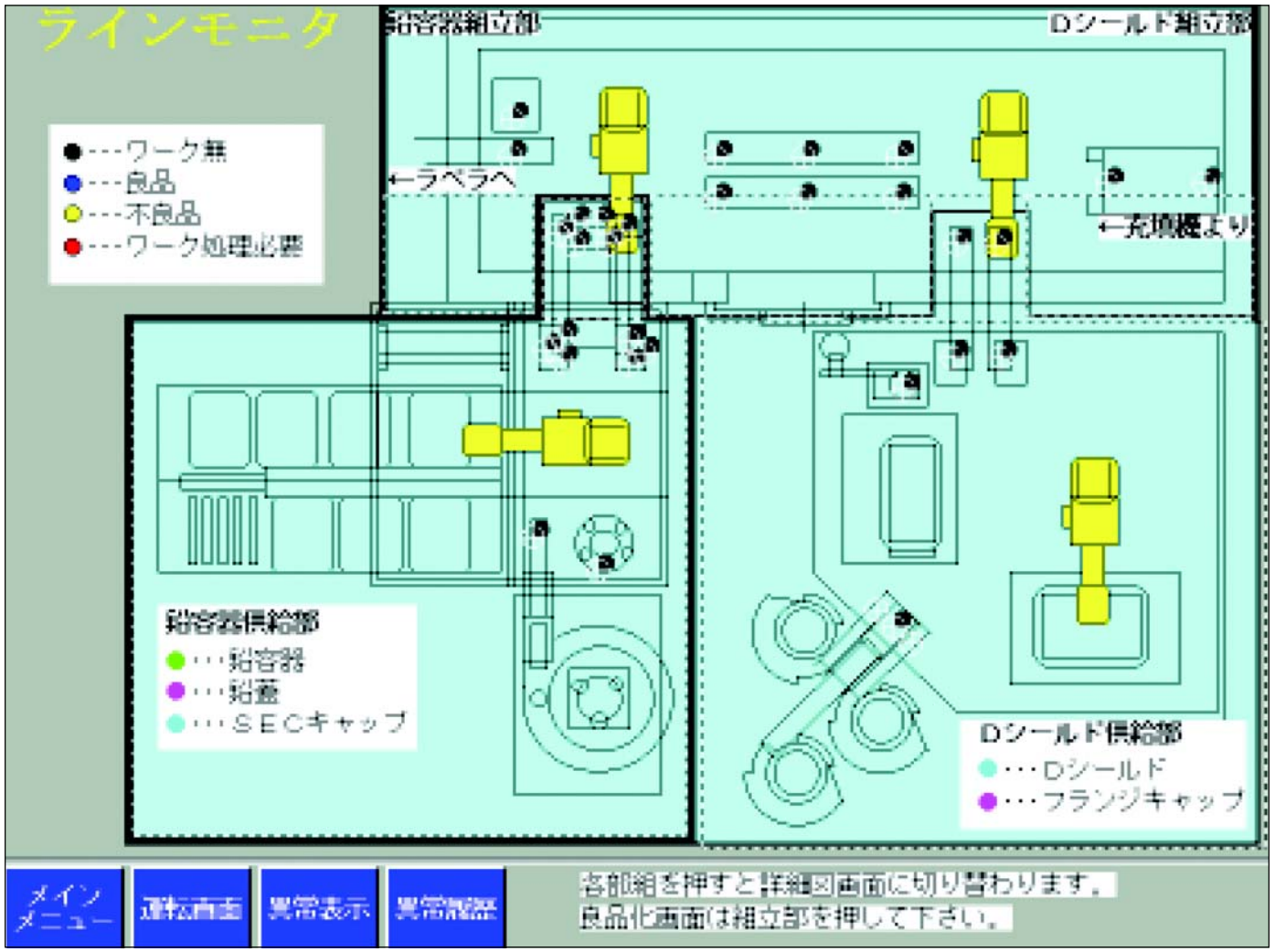

Figure 9. Status Monitoring.

able components stocked on commercial trays returned from hospitals. The robot acknowledges the position of the reusable components through imaging. Then, the robot conducts all necessary inspections and transfers only the good reusable components inside the lead shielding - *Figures 7 and 8.*

This machine can store enough material/components for the production of one lot so that operators do not need to manually feed materials into the system during production. This feature improves the utilization of manpower by enabling a single operator to run and manage two lines running simultaneously.

Fully Automatic Correction and/or Rejection of Non-Conforming Product

With conventional production lines where the emphasis is on production efficiency, automatic rejection of defective product is a rather common feature. In the case of radiopharmaceuticals; however, product bottles containing drugs cannot be simply discarded if the defect is only associated with the exterior package. Therefore, the defective packaging will be corrected.

In the system being described in this article, the operator's control screen continuously displays the quality and status of products being transferred or assembled at each section of the machine as they are monitored by on-line sensors - *Figure 9*. If a product defect is detected at one of the automatic inspection stations, the machine automatically attempts to correct the defect. If the defect can not be corrected, the machine stops temporarily. During this stoppage, the operator checks the condition of the product and can manually correct the defects if necessary through inputs made at the operator panel. The system automatically records by whom, when, and how the change was made for subsequent analysis of the operation. The security function requires operators to enter employer identification number or password so that only authorized personnel can operate the machine, thus preventing unauthorized access.

Operations that require opening of lead-shielding during production should be kept at minimum to avoid radiation exposure. Defective parts such as syringe, including those for which manual operator correction was attempted, are put into final lead-shielded containers. However, the plastic cap will not be placed on the defective goods so that they can easily be differentiated from acceptable finished goods. All defective product, once safely packed into a shielded container, is automatically removed from the lead-shielded area around the processing line and placed in a holding container for future disposition.

Advanced Production Management System

Radiopharmaceutical products are manufactured only upon receipt of orders due to their short useful lifespan. The same product may be manufactured several times a day, but each production lot is relatively small. Radiopharmaceutical products of different radiation doses may be prepared all simultaneously, and labeled as a single lot. If the production involves manufacturing different radiation doses of products, the

Figure 10. Production management screen.

filling volume of the radiopharmaceutical is changed as necessary and the radiation dose contained in each unit is printed onto the labels placed upon the syringes and product containers. The packaging line automatically and continuously outputs the products based upon an operation program in conjunction with the filling machine, which is capable of changing volume instantly and automatically according to the program. Needless to say, several QC units are manufactured for each lot, separated from actual products, and stored for analysis. Figure 10 indicates the screen of production management.

The production of radiopharmaceuticals requires operators to have a high skill level and a great deal of familiarity with the system because of the unique safety and quality requirements of these products. Therefore, it is essential to develop a well-designed production management system and a reliable production support system. A consistent production process management system is provided to cover all aspects of manufacturing from filling to packaging. At the beginning of a production process, operators are requested to enter their employee identification information or passwords for identification purposes. At the end of production, a pro-

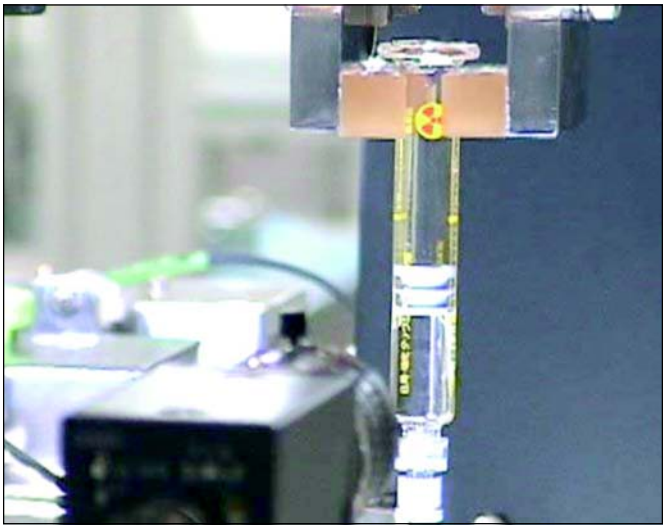

Figure 11. Syringe product volume inspection.

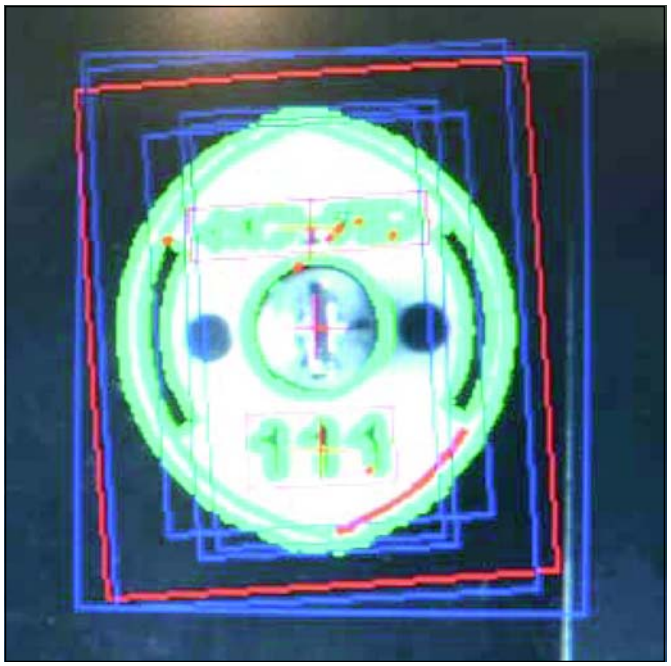

Figure 12. Syringe cap inspection.

duction log which contains manufacturing information required for the product batch record is printed.

In Figure 11, the fill volume of a syringe product is inspected through image processing. When the amount of the radiation dose required for a unit is changed, this feature can double-check the operational setting. Figure 12 shows the inspection of a syringe cap label indicating the radiation dose. The products go through a final check after being packaged into its exterior container.

Discussion

The fundamental planning of a robot-based automated processing line must begin with a well-defined basic concept. Upon completion of an initial conceptual design, simulation testing involving only the robotics are done to confirm the line output and to verify both robot accessibility and to identify any obstacles to robot operation. Image processing necessary for inspection also is thoroughly tested to ensure proper and efficient operation.

Upon successful completion of this evaluation phase, the final conceptual design is established. Following completion and approval of the final conceptual design, the detailed machine design phase begins. In this process development approach, a relatively longer time is allocated for the initial and final conceptual design stage, but as a result, less post-assembly fine adjustment is required than in a more conventional design and development approach. Using a conventional approach, problems are too often discovered after final assembly of equipment rather than at the machine design stage. Using our approach of extremely careful process development and design, we have more confidence that the first machine will provide complete and fully satisfactory operation meeting all user requirement specifications.

Nearly all "bugs" in robotic programming also are eliminated before delivery, minimizing the time required for installation and set up at the factory site. In fact, in the case study presented in this report, it took approximately one month for the installation and set up to stabilize operation of this system. We believe that installation and set up for a system of this complexity could take six months or longer for a conventional machine-based systems. As a further benefit of the detailed and thorough design approach and documentation, it took roughly two weeks for three workers to complete all IQs/OQs.

Additionally, this robot-based system can handle operations that are not possible with conventional machine-based systems and that may have to be done manually by personnel. Therefore, the overall operation has become less labor intensive, resulting in less operational cost. It should be noted that operator safety and product quality have been improved as a result of the utilization of vision systems. Also, the occurrence of line stoppages has been reduced to nearly zero because defective components or products are identified beforehand.

Finally, we have observed no accelerated deterioration of the robot as a result of exposure to radiation. Some of the robot movements can be set at relatively low speed, thus increasing stability and reliability. Our experience has shown that as a further advantage robotic systems, such as the one described herein, can provide significant advantages in the long run because of the ability to accommodate changes of product and parts.

Conclusion

The new technology introduced here is a highly automated, robotic packaging line for radiopharmaceuticals. The filling section of this parenteral drug production line employs an isolator system decontaminated by vapor hydrogen peroxide. The concept introduced here also can be applied to a filling system by utilizing vapor phase hydrogen peroxide resistant robots operating within isolator systems.

The marriage of very high technology, automated aseptic processing in an isolator with robotic assembly and inspection of the final product provides an efficient, high quality, and very safe manufacturing system for radiopharmaceuticals. This approach manages risk very effectively and as such is fully compliant with the FDA's current emphasis on risk mitigation in pharmaceutical manufacturing.

In our view, this technology can be more broadly applied not only to highly specialized products such as radiopharmaceuticals, but to more conventional sterile pharmaceutical preparations.

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This article describes a pragmatic and effective approach to network qualification compliance.

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Establishing Compliance of a Company's IT Infrastructure - A Practical Guide to Meeting GxP Requirements

by John Andrews and Richard Labib

Introduction

As the world of computing continues to expand relentlessly from the humble word processors of approximately 10 years ago to the interactive web enabled world of today, the functional boundaries between computer applications and the software/hardware components of the infrastructure are becoming harder to differentiate. The healthcare industry requirements to demonstrate compliance and control of these essential elements have never been so important.

Traditionally, computer applications are subject to validation, a process that involves producing written evidence that a particular software application was planned, specified, developed, and tested against a predetermined software development lifecycle. There are many software development lifecycle models to choose from such as the ISPE Good Automated Manufacturing Practice (GAMP) V model or the Institute of Electrical and Electronic Engineers (IEEE) waterfall model. These development models intend to provide a quality assurance framework of control around the development of something that is intangible, i.e., software.

However, for the IT infrastructure of a healthcare company, these rigid development models for software development are not suitable to validate a company IT network. In fact, it is almost impossible to validate the IT infrastructure because of the changing nature of the very elements that make the network perform. To validate a software application, first you must know and control the versions under development and after implementation the maintenance of the applications. For the infrastructure, this is more difficult because of the dynamic nature of the network elements (hardware and software) and the non-deterministic nature of some of the network communication protocols employed, making it very difficult to validate, therefore, another term must be adopted i.e. "Under Compliance."

"Under Compliance" means that the planning, organization, installation, use, and maintenance of the IT infrastructure is controlled and documented, therefore achieving the same objectives of validation without having to freeze the entire infrastructure network while the

Table A. OSI reference model: network layers.

Layer	Layer Name	Layer Function
7	Application	Interfaces directly with the application programs running on the network. This layer provides services such as file access and transfers, peer-to-peer communication and resources sharing.
6	Presentation	Translation of data formats to enable computers using contrasting languages to communicate. Data encryption is handled in this layer.
5	Session	Establishes bi-directional communication between applications using conversational techniques or dialogues.
4	Transport	Ensures reliable message delivery and control of data between systems in flow packets.
3	Network	Standardization of addressing mode between multiple, linked networks and services to ensure packets of information arrive at the correct destination.
2	Data Link	Defines the control of communication between two devices directly linked together and the packet and framing methods.
1	Physical	Defines the mechanical components, type of medium, transmission method and rate available.

Basic Element	How Addressed
1. LAN Support Documentation	How to write LAN Support Documents: this document would provide guidance on the development of infrastructure drawings for both the overall site and building layouts, the development and maintenance of closet connection drawings, PC desk top build standards, device inventory, specifications for device environment and supplies, and device level documentation and qualification scripts.
2. Qualification Planning and Execution	Qualification Plan Template Qualification ActivitiesTable Template Qualification Report Template
3. Procedures	The following is a list of recommended procedures necessary to support the qualification status of the network. Some are obviously a higher priority than others, but they are all necessary to demonstrate that the infrastructure is under control. • Installation of Network Devices • Escalation and Call-Out • Change Control (Hardware and Software) • Security • Preventative or Routine Maintenance • Problem Investigation • Training • Start-Up/Shutdown • Performance Measuring • Capacity Management • Help-Desk • User Account Management • Management of Virus • Back-Up Management • Configurations Management • Disaster Recovery • Archiving • De-Commissioning
4. Acceptance Testing	This takes the form of a device Installation and Operational Qualification script and a LAN Operational Qualification script, which would be referenced by the Network Device Delivery Item List folder.
5. Training of Support Personnel	Site training record retention. This should conform to the relevant company policy for documenting training records.
6. Security	This should reference the company's policy for IT security.
7. Network Recovery	LAN Escalation and Call-out guidelines
8. Change Control	LAN Change Management procedure
9. Periodic Review	Each company site must establish periodic review process.
10. Qualification Documentation	Each company site must describe how Qualification documentation will be stored, managed, etc.

Table B. The basic 10 elements of the network qualification and the network support.

validation activity is underway. This approach builds on the GAMP software and hardware category principles, which state that standard software applications and standard hardware should be documented against the needs of the user and records maintained of installed and configured devices.

The Method

In order to understand the GAMP software and hardware category approach to compliance, the Open Systems Interconnection (OSI) reference model first must be understood. This model breaks down the network into discrete layers from operating systems that form the basis of the network topology to the applications that run on the servers themselves – *Table A*.

Layers 1, 2, 3, and 4 (e.g. intelligent bridges and routers) belong to GAMP software Category 2 for software and GAMP hardware Category 1 for hardware, where the recommended approach is to record firmware versions and configuration settings and verify operation against user requirements. The hardware should be checked to confirm with given standards and drawings and this activity should form the basis of the network IQ.

Layers 5 and 6 (i.e. network operating systems) belong to GAMP software Category 1 for software, where the recommended approach is to record version (including service pack). The Operating Systems will be challenged indirectly by functionally testing of the network devices.

It should be noted for the purposes of this article, the approach to bring a company's Wide Area Network (WAN) "Under Compliance" would not be addressed. However, by ensuring that each company's site Local Area Network (LAN) is "Under Compliance," it only would require a small amount of additional effort, following these principles, to achieve compliance for the WAN.

In practical terms, to demonstrate compliance with cGxP requirements, you must demonstrate an environment of being "Under Compliance" as mentioned above. This involves developing, training, and using a "LAN Qualification Tool Kit." The "LAN Qualification Tool Kit" characterizes requirements for defining what a LAN Qualification is and how the IT group maintains the "Under Compliance" status. This involves:

- a definition of LAN Qualification and planning for compliance
- identifying the minimum set of required documentation (LAN components and LAN support processes) required for the LAN Qualification
- standardizing documentation content and format to support day-to-day activities
- develop templates, examples, etc. to expedite the IT infrastructure qualification process

The "LAN Qualification Tool Kit allows a company to demonstrate being "Under Compliance" by addressing 10 Basic Elements of the Network Qualification and Network Support - *Table B*.

The 10 Basic Elements of the Network Qualification come together to address four very important phases, e.g. the Network Plan and Design Phase, the Devices Installation Phase, the Qualification Phase, and the Operational Phase - *Figure 1.* However, within the Operational Phase, it must be accepted that the network, as an entity, is never finalized, e.g., continually evolving and being maintained and therefore unable to version control overall as discussed previously.

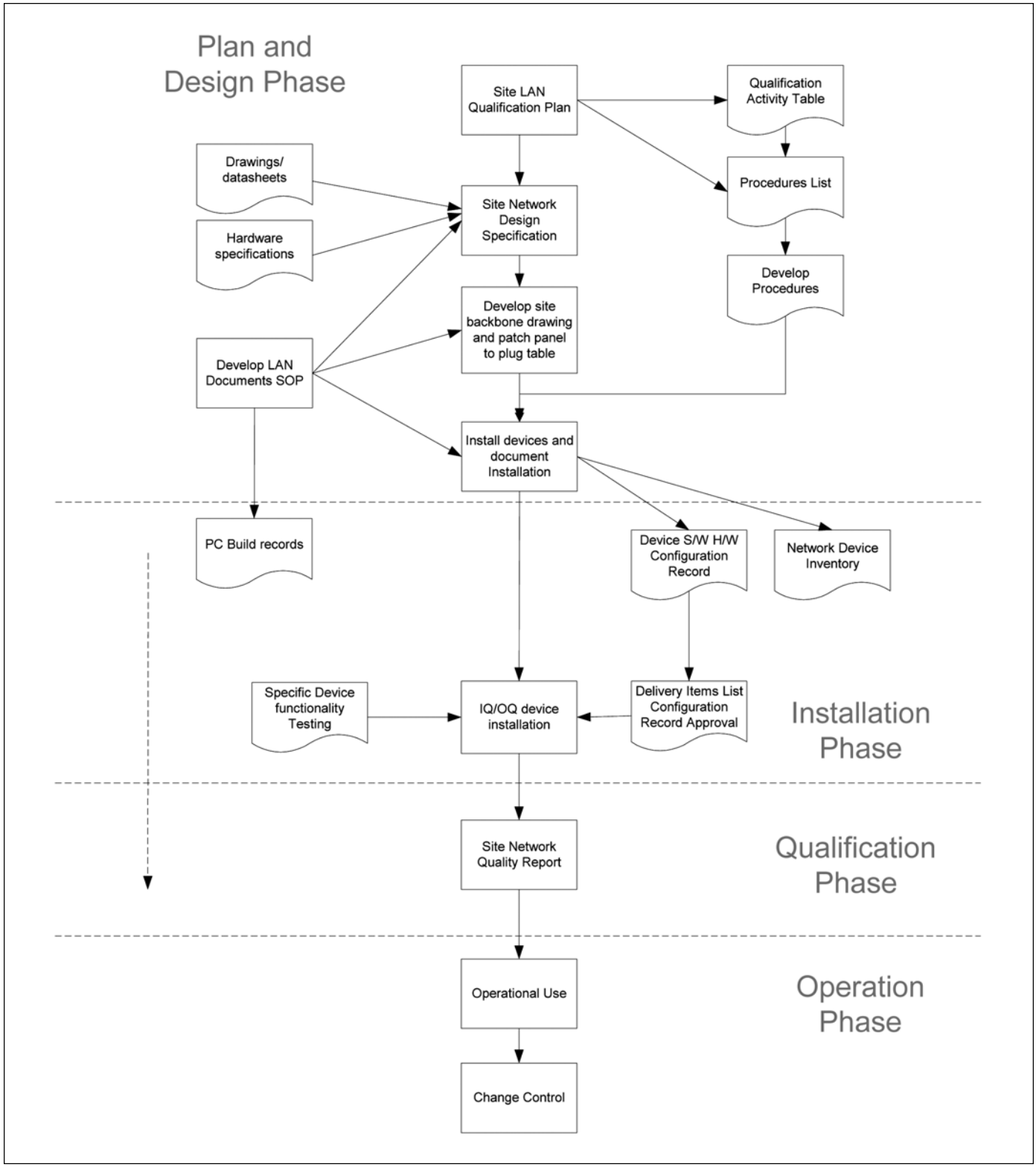

Figure 1. Network qualification overview.

Basic Element 1 - LAN Support Documentation

Infrastructure Drawings

The Infrastructure drawings will start with the WAN backbone and show how the sites are interconnected. Each site drawing will then show how each site network connects up to the WAN backbone. With this slight overlap, a node can be traced all the way through the network. This will document the Network to the closet level. From there, As-Builts will be used to map a workstation grid to a patch panel and then the Network Professional can trace to a switch port. This information will be signed, dated, and filed for ready access.

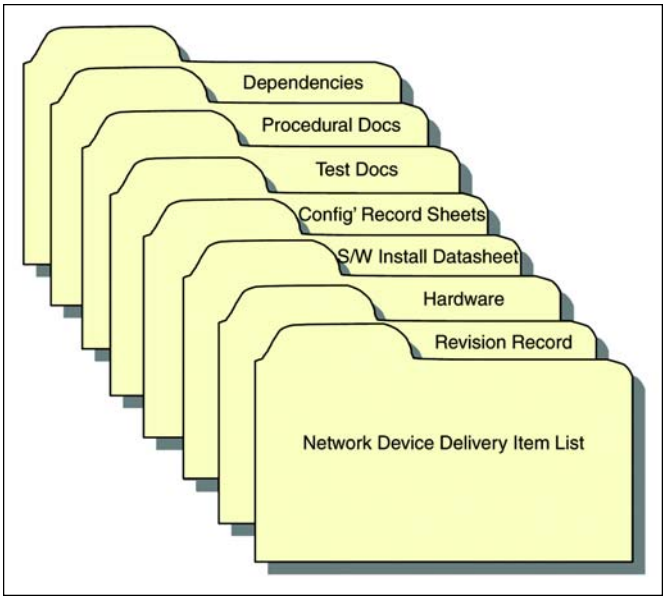

Figure 2. Network device delivery item list folder.

Electronic signing and storage may be used per site requirements.

Closet Connection Drawings

As Grids are added and deleted, when appropriate, updated connection drawings will be produced on a daily basis.

After connection drawings are updated, print and add approval with date and time of printing and signing and add to the relevant closet configuration qualification Folder. Periodically, audit to ensure accuracy of all connection drawings for Grids and their locations. Update connection drawings as necessary.

If cables are not embedded into the walls of the building, and they are clearly visible, an alternative approach could be used. Table C shows how a simple table can define where the outlet from a patch panel can be found within the building, and also allows for traceability of multiple Virtual Local Area Networks (VLANS).

PC Desktop Build Standards

Standard desktop PC/laptop configurations/builds should be defined. These standard builds must be tested and the results kept in accordance with good testing practices, e.g., against approved specifications and in accordance with cGxP practices. Installation of PC/laptop configurations/builds is conducted against an approved operating procedure. Records of each PC/laptop builds are maintained and controlled. There also should be an appropriate IT security policy that covers user's use of downloads or non-standard applications.

Device Inventory

Each site will need to maintain a site inventory list. It can be a spreadsheet or a database - *Table D.* Required fields include:

- Device Inventory Number
- Device Name
- Make
- Model
- Serial Number
- Location
- Date Placed in Service

Specifications for Device Environment and Supplies

The supplier's technical documentation should be reviewed to obtain the following details concerning the operating environment for the network devices. The following topics should be considered when sighting network equipment:

- Temperature
- Humidity
- External Interference
- Physical Security
- Radio-frequency, electromagnetic and UV-interference
- Electrical Supplies, e.g., filtering, loading, earthing, Uninterruptible Power Supplies (UPS) requirements, disconnection by fault

Confirmation that the installed devices comply with these recommendations should be formally documented.

Device Level Documentation

Each device in the network should be documented with a unique configuration file name and number that will conform to the sites naming standard, this documentation will be under revision control. Use the document which specifies the detail relating to the device using a device Network Delivery Item List (to be discussed later) and the relevant Device Installation (IQ) Test Scripts and the Testing Device (OQ) Test Scripts to document the correct installation and operation of the device on to the network. The device configuration settings are recorded, either on paper or to a configuration file located in a protected area of the IT department network or a database.

Qualification Scripts

Qualification scripts should be prepared against a procedure designed to ensure that the design requirements for the network are considered and documented, the network drawings are complete and under control, that testing of each installed device is in accordance with the expected performance, and that procedures to support the network development and management are available. This approach will confirm that the network is qualified ready for use by validated applications.

Network Device Delivery Item List

The Network Device Delivery Item List forms the basis for configuration management of all the documentation, software items, and support procedures that are needed to support a network device. This Network Device Delivery Item List should be structured to form a compliance folder that would live with the network device, i.e., a network server.

This folder would contain or reference all the required documentary evidence necessary to demonstrate that device is "Under Compliance." Sections of the folder should include:

- a Revision Record Sheet, covering the versions of the Network Device Delivery Item List
- a Hardware Datasheet, covering the specification of hardware item that has been installed
- a Software Install Datasheet, detailing software name, version number, build record etc.
- Configuration Record Sheets, covering the configuration details for the network device
- Test Documentation, reference to any functionality test scripts that support IO/Q of the device qualification
- Procedural Documentation, reference to all relevant procedures needed to support the operation, maintenance and compliance of the network device
- Dependencies, list any hardware, software, or other dependencies, which are not part of this installation that may impact the compliance of the device, including any known errors (and workarounds) and pending change requests

The Network Device Delivery Item List Folder (Figure 2) is the pivotal document to the maintenance of the network device qualification. It is intended to be a live dynamic document that should be referenced as part of any activity associated with the device. This includes that most minor configuration change. Should these minor activities happen without updating the associated records then it wouldn't be long before the qualification status of the whole LAN could be brought into question.

Basic Element 2 - Qualification Planning and Execution

Qualification Plan

A Qualification Plan is needed to summarize the defined approach to meeting the compliance requirements for the infrastructure qualification activities. This plan should detail the 10 basic element approach to network plan/design, device installation, and the network qualification. It should detail who is responsible and what deliverable will be produced. This document must be approved by relevant individuals such as the IT manager responsible for the IT infrastructure, QA, and the site senior management.

Qualification Activities Table

A Qualification Activity table may be used to track who is responsible for producing and managing each specific deliverable and their progress. This activity table can be used to support the Qualification Plan and the management of the qualification project.

Qualification Report

Once all the activities detailed in the Qualification Plan have been completed and supported by the completion of the Qualification Activity table, a LAN Qualification Report can be produced. This report confirms that the LAN is suitably "Under Compliance" and the relevant support procedures and guidelines are available and support staff is trained to support the future compliance status of the network. This report confirms that the existing system is qualified and details how this status will be maintained linking the ongoing qualification activities associated with operational compliance.

Patch Panel ID - 101		
VLAN ID	**Patch Panel Port ID**	**Building Room ID**
01	101-001	Clean H7
01	101-002	Clean H7
01	101-003	Clean H7
01	101-004	Clean H7
01	101-005	Clean H4
01	101-006	Clean H4
02	101-007	IT A1
01	101-008	IT A2

Table C. Connection table.

Basic Element 3 - Procedures

Procedures are an essential part of the compliance assurance process, without them in place the demonstration of being "Under Compliance" would be impossible to accomplish. Each site's procedural requirement should be based on the checklist of example procedures listed above and an assessment of the company's current working practices. Gaps in procedural coverage should be addressed with the members of the IT departments support staff, after all they ultimately will be the ones who will have to adopt these ways of working. This can be achieved with the aid of facilitated workshop sessions, where the facilitator is a compliance expert and understands what each of the procedures should address.

Basic Element 4 - Acceptance Testing

All installed LAN components are tested in accordance with specific device testing protocols, developed as standard for each type of device. Acceptance Testing also will be demonstrated by the fact that the LAN is operating normally. Testing documentation includes expected and actual results, the name of the person who performed the tests, the date the tests were performed, and verification that the results meet the acceptance criteria. Disruptive testing should be avoided wherever possible.

For IQ, this testing could include:

- Network Device Delivery Item List Folder is complete and available for the installed device
- Procedure Verification for all relevant procedures to manage the use and maintenance of the device
- Hardware Configuration and Inventory Verification
- Connections and Cabling is connected and suitably documented
- Power Supply Requirements Verification

- Maintenance
- Training and Documentation Verification
- Software Procedure Verification for all relevant procedures to manage the use and maintenance of the device
- Software Backup and Inventory Verification
- Software Installation and Version Verification
- Software Configuration Verification

For OQ, this testing could include:

- Contingency and Disaster Recovery Plan(s) Inspection
- Start-Up and Shut-Down Testing
- Emergency Power Verification
- Operational Security Tests
- System Backup and Archive
- File Restoration Test
- Device Operating Normally Test
- LAN Backbone Functional Test (LAN OQ)

Basic Element 5 - Training of Support Personnel

The training records of all IT Infrastructure support personnel should be organized and filed according to each company/site requirements, ensuring that all relevant procedures have been trained to these members of staff. CV also should be filed with these records because technical qualifications and experience is vital to provide the relevant compliance assurance to a potential auditor of the "Under Compliance" methodology.

Basic Element 6 - Security

Ensure that physical and logical access to network components are in compliance with the companies' IT Security Policy and Standards and fully integrated into the organization's overall security philosophy. Guidance on how to apply an integrated approach to security from setting a security policy to business continuity planning can be sorted from applying the principles defined within BS ISO/IEC 17799:2000. As part of device selection a full assessment against the requirements of 21 CFR Part 11 is a necessity.

Physical Network Device Security

Devices should be kept behind a locked door and/or in a locked cabinet.

Electronic Administrative Access

It is recommended, that when possible, access will be limited by user account and password maintained in security servers with fallback password(s) documented and placed in a lockbox in the event that the security server is unavailable for user authentication.

Basic Element 7 - Network Recovery

An assessment of the availability and effectiveness of the guidelines and procedures governing network recovery should be made and documented. This assessment should cover:

- Back-up taking
- Data recovery from back-ups
- Procedure for escalation and call-out
- Procedures for business continuity
- Testing of UPS (if necessary)
- Service Level Agreement (SLA)

Basic Element 8 - Change Control

Ensure change management procedures exist to manage changes to the network and that this is conducted in a controlled and documented manner.

Basic Element 9 - Periodic Review

Periodic review of the methodology and associated documentation is vital to ensure all relevant procedures are being correctly followed and the documentation is current and relevant. A plan also should exist that details who will perform the review, and what schedule will be followed (monthly, annually etc.). This plan also should specify any specific areas for consideration such as availability of configuration records for the network devices, i.e., based on a weakness trend observed during previous reviews.

Basic Element 10 - Qualification Documentation

The approach to the management, storage, archival, and retrieval of qualification documentation is vital to the success of the methodology; this includes all documents generated from initial qualification, change control documentation, and periodic review reports. It is suggested that it is best to separate the documentation into the documents that are needed to support the maintenance of the system and the results from testing activities, which could be archived along with all other validation documentation.

Summary

It is a well known fact that it is not possible to validate an IT Infrastructure; however, it is possible to achieve a state of being "Under Compliance" which involves applying a methodical procedural framework to control the Network Planning and Design, Devices Installation/Qualification, and the

Device Inventory Number	Device Name	Make	Model	Serial Number	Location	Date placed in service
00260	EUFRL204	HP	Vectra VLI8	FR94428069	Data Centre	04 Nov 1999
00261	EUFRLN10	Cisco	Catalist 4506	FOC072105LW	Bld 10	11 Aug 2003
00262	EUFRLN15	Cisco	Catalist 3620	FOC0720W19Q	Bld 3	25 May 2002

Table D. Example device inventory.

Operational activities.

Devices must be assessed against their level of configuration/set-up necessary to integrate them into the working IT network and controlled in accordance with their own specific Network Delivery Item List folder, which manages the configuration management aspects of all the elements of the IT infrastructure.

Supplier's documentation is leveraged as much as possible to provide evidence of system specifications as well as utilizing standard qualification and test scripts that are based on what an IT manager would currently expect to be done.

The whole methodology is held together via a 10 basic element checklist which covers all the main aspects of system qualification by drawing on a pragmatic approach to compliance without getting tied up with the impractical aspects of validation.

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1. *GAMP 4, Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems,* Version 4.0, December 2001, ISPE.

2. BS ISO/IEC 17799:2000 Information Management Security.

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John Andrews is a Director of Andrews Consulting Enterprises Ltd. Prior to this, he was the manager of IT consulting service at KMI, a division of PAREXEL International LLC. He is a member of the GAMP 4 Special Interest Group on Process Control; he also sat on the Editorial Board for GAMP 4. His responsibilities include providing consultancy on computer systems validation, compliance, and quality assurance activities within the pharmaceutical, biopharmaceutical, medical device, and other regulated healthcare industries. Prior to that, he held positions as computer system validation manager and supply chain systems project manager with GlaxoSmithKline. Responsibilities there included all aspects of computer systems validation, from process control through to business and laboratory system Validation. Managing teams with responsibilities for ensuring all computer system validation activities undertaken on site and within projects are to an appropriate level to comply with the regulator's requirements. Previous employment includes 15 years with SmithKline Beecham Pharmaceuticals where he held positions as a senior engineering standards engineer, secondary manufacturing electrical engineer, projects engineer, and electrical supervisor. He can be contacted by telephone: +44-7867513519 or by e-mail: john.andrews2@ntlworld.com.

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This article presents a commercial software to design, simulate, and optimize the production of a large-scale monoclonal antibody.

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Design, Simulation, and Optimization of a Large-Scale Monoclonal Antibody Production Plant: Upstream Design

by Steve K.W. Oh, K.H. Kuek, and Victor V.T. Wong

Introduction

Monoclonal antibodies (Mabs) have become the most rapidly growing class of pharmaceuticals for diagnosing and treating a wide variety of human disease, including cancer.[1]

To produce sufficient amounts of Mabs, large-scale cultivation of mammalian cells for the production of Mabs has become one of the top priorities in the biopharmaceutical industry. Process simulation can be useful for the development, evaluation, and scale up of the plant design, reducing expensive and time-consuming laboratory and pilot plant testing. The original version of Superpro 4.9 was developed at the Massachusetts Institute of Technology (MIT) in the late 1980s to address the needs of the biopharmaceutical industries.[2] It was used to simulate a monoclonal antibody production plant. A flow sheet was built from which the process simulator would be able to determine at an early stage whether it would be economically feasible to build the plant. In this study, the material balance coefficients required by the software to simulate the process were determined from experiments. After developing the base-case model using the process simulator, the feasibility of alternative process setups and operating conditions was explored. We used our model to debottleneck the production schedule in order to evaluate possible capacity expansion options.

Materials and Methods

The model cell line used in this work was the murine hybridoma, CRL1606, which secretes an immunoglobulin, IgG, against human fibronectin. CRL1606 was maintained in a serum-free media supplemented with 2-mercaptoethanol (35µl/l), insulin (10mg/l), transferrin (5.5mg/l), ethanolamine (2.44µl/l), and bovine serum albumin (7.5mg/l). The suspension culture was passaged every two days by inoculating at 2×10^5cells/L into fresh media and incubating at 37°C, 8% v/v CO_2.[3] Pluronic F68 (0.01% v/v) was added to minimize shear damage to the cells. Cell density and viability was determined using a haemocytometer coupled with trypan blue staining. Samples of the culture were taken daily and stored at -20°C for later analysis. Glucose, lactate, glutamine, and glutamate concentrations were measured with a biochemical analyzer. Amino acid concentrations were analyzed by high performance liquid chromatography using a reverse phase column. Amino acid derivatization prior to the HPLC analysis was performed using a reagent kit. Detection was done at 395 nm

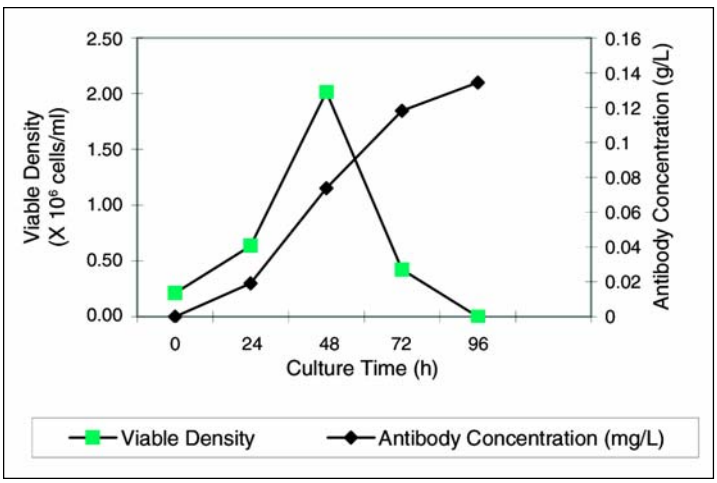

Figure 1. Viable cell density and antibody concentration during batch growth of the hybridoma CRL1606 in serum free medium.

Amino Acids	Concentration			
	(mM)		Produced	Consumed
	t=0h	t=96h	g/L	g/L
Aspartic acid	0.29	0.18		-0.014
Glutamic acid	0.60	0.64	0.0057	
Asparagine	0.27	0.00		-0.0359
Serine	0.47	0.18		-0.0310
Histidine	0.23	0.15		-0.0118
Glutamine	2.90	0.00		-0.4237
Glycine	0.49	0.71	0.0167	
Arginine	0.48	0.23		-0.0435
Threonine	0.66	0.62		-0.0047
Alanine	0.34	2.78	0.217	
Proline	0.41	0.51	0.0119	
Cysteine	-	-	-	-
Tyrosine	0.49	0.33		-0.0284
Valine	0.95	0.56		-0.0458
Methionine	0.26	0.00		-0.0381
Lysine	0.95	0.60		-0.0505
Isoleucine	0.96	0.49		-0.0612
Leucine	0.93	0.37		-0.0733
Phenylalanine	0.47	0.32		-0.0247
Tryptophan	-	-	-	-
Amino Acid Produced			**0.2514**	
Amino Acid Consumed				**-0.8865**

Table A. Amino acids analyses.

with a fluorescent detector. Antibody concentration was determined by an enzyme-linked immunosorbent assay described elsewhere.[3]

Experimental Results

Figure 1 shows the typical growth profile of CRL1606. The maximum viable cell density achieved in batch culture was 2×10^9 cells/L, a cell density change of 1.8×10^9 cells/L. This difference was calculated by subtracting the initial inoculum size from the maximum viable cell density.

Glucose consumption was measured by taking the difference between the initial and final glucose concentration. The initial glucose concentration was 4.52 g/L and the final glucose concentration was 2 g/L, giving a glucose consumption value of 2.52 g/L over the 96-hour period.

However, determining the uptake of amino acids was not as straightforward since certain amino acids were consumed (e.g., glutamine) while others were produced (e.g., alanine). The total amino acid concentration in g/L (both produced and consumed) was calculated mathematically using the expression $\Sigma\Delta\,(\text{AminoAcids})_i$. As the HPLC method used could not detect cysteine and tryptophan, these were excluded from the analysis. Table A shows the results of the amino acids analyses. Amino acids were measured in mM and converted to g/L for input into the simulation. The total amount of amino acid showing a net production (i.e., glutamate, glycine, alanine and proline) over the 96-hour period was 0.25 g/L, while the amount of lactate produced was 1.7g/L. The total amount of amino acid consumed was 0.89 g/L. For the purpose of this simulation, the amount of amino acid produced was lumped together with the lactate as a "waste" term in the mass balance.

Components	Concentration of Product Consumed or Secreted (g/L)
Glucose	-2.52
Amino Acids Consumed	-0.8865
Wastes (A.A produced + Lactate)	1.95
IgG	0.13
O_2	-1.95×10^{-4}
CO_2	2.68×10^{-4}
Number of cells produced = 1.8×10^9 cells/L	

Table B. Concentration of materials consumed or produced.

ELISA was performed on the supernatants collected and the antibody content at the end of 96 hours was found to be 0.13 g/L - *Figure 1*.

The ash-free biomass was calculated from the dry cell mass and was found to be 1.5×10^{-11} g/cell.[4] Table B summarizes the parameters used in the simulation. CO_2 production was assumed to be the same as O_2 consumption, at a rate of 1 nmol/min for 1.7×10^6 cells/ml of cell culture,[5] which results in an oxygen consumption of 1.95×10^{-4} g/L for a cell density of 1.8×10^9 cells/L over the 96-hour period.

The coefficients of the mass balance were defined as follows:[6]

$$\theta_p = \frac{\text{Grams of product secreted or substrate consumed}}{\text{Number of cells produced}}$$

Based on the results of these experiments, the following mass balance was derived:

14 Glucose + 4.92 Amino Acids + 0.00108 Oxygen
= 0.15 Biomass + 0.72 IgG + 10.83 Waste +
0.00108 Carbon Dioxide + 7.22 Water (Eq1)

Since supplements such as 2-mercaptoethanol, insulin, transferrin, 2-aminoethanol, and protease-free BSA are not considered to be nutritive, they were excluded from the mass balance. The equation was balanced by including water produced by respiration on the right hand side of the equation.

In the simulation, the amount of raw materials fed into the bioreactor was scaled-up based on the amount of glucose, amino acids, and other supplements in the culture medium. For instance, the glucose concentration in the medium was 4.52 g/L; hence, a single 100L seed fermenter would require 0.452 kg/batch of glucose. Similarly, the total amino acid concentration in the medium was 1.736 g/L. Thus, for a single batch, the 100L seed fermenter would require 0.1736 kg/batch of amino acids. The amount of supplements (e.g., salts, insulin, transferrin) fed was 0.0135 kg/batch for the 100L fermenter. As the culture volume in the fermenter was limited to 85% of vessel capacity, the amount of Water-For-Injection (WFI) fed into the 100L fermenter was 85kg/batch. For the 1,000L and 10,000L fermenter, these values were multiplied by a factor of 10 and 100 respectively - *Table C*.

Simulation Model

By selecting the required unit procedures and connecting them with the material flow streams, a batch process simulation model was developed in the software. Pure components, such as biomass, glucose, and WFI were already registered in the software's default databank. Components

such as amino acids and IgG had to be defined separately as they were not included in the default databank.

Figure 2 is a screen-capture image of the process flow diagram created in the software showing the 10,000L fermenter. The process scale up from 100L to 1,000L and finally to 10,000L fermenter can be briefly described as follows. Glucose, amino acids, and supplements were dissolved in WFI and transferred into the blending tank (V-101). A mixer (MX-101) was used so that the four raw material streams could be mixed and transferred into the blending tank in a single stream via a single pump (PM-101). This sequence of operations for blending the media included all charges and transfers and took approximately 8.5 hours.

The media was then sterile-filtered with a dead end filter (DE-101) before transferring into the 100L seed fermenter (V-102). Biomass, seeded at a density of 2×10^8 cells/L, was then charged into V-102. Incubation was then carried out at a constant temperature of 37°C. The extent of reaction was set at 95% for a process time of 96 hours with a turnaround time of 24 hours. The mass balance coefficients were specified in Equation 1. Carbon dioxide produced from the culture was vented through port S-108. After 96 hours, the contents of V-102 were transferred into the 1,000L fermenter (V-103). Additional glucose, amino acids, supplements, and WFI was charged into V-103 via the second blending tank (V-104). Meanwhile, V-103 was cleaned and sterilized in preparation for the next batch. After the culture in V-103 had grown to the required cell density, the contents were transferred into the 10,000L fermenter (V-106). Following that, all the culture in the 10,000L fermenter was filtered through a dead-end filter (DE-104) to remove all the cells and debris in the culture and transferred out to a final storage tank (V-107).

Components	100L	(kg/batch) 1,000L	10,000L
Glucose	0.452	4.52	45.2
Amino Acids	0.1736	1.736	17.36
Supplements	0.0135	0.135	1.35
WFI	85	850	8500

Table C. Inputs for simulation.

The final storage tank (P-33/V-107) was used to store the supernatant containing unpurified antibody. The unpurified product was cooled to 4°C to prevent product degradation, and to prepare it for subsequent purification steps. This product was transferred out through stream S-149, which was specified as our revenue stream in this simulation.

After designing the flow-sheet, each of the unit procedures was initialized by completing all the relevant Input/Output

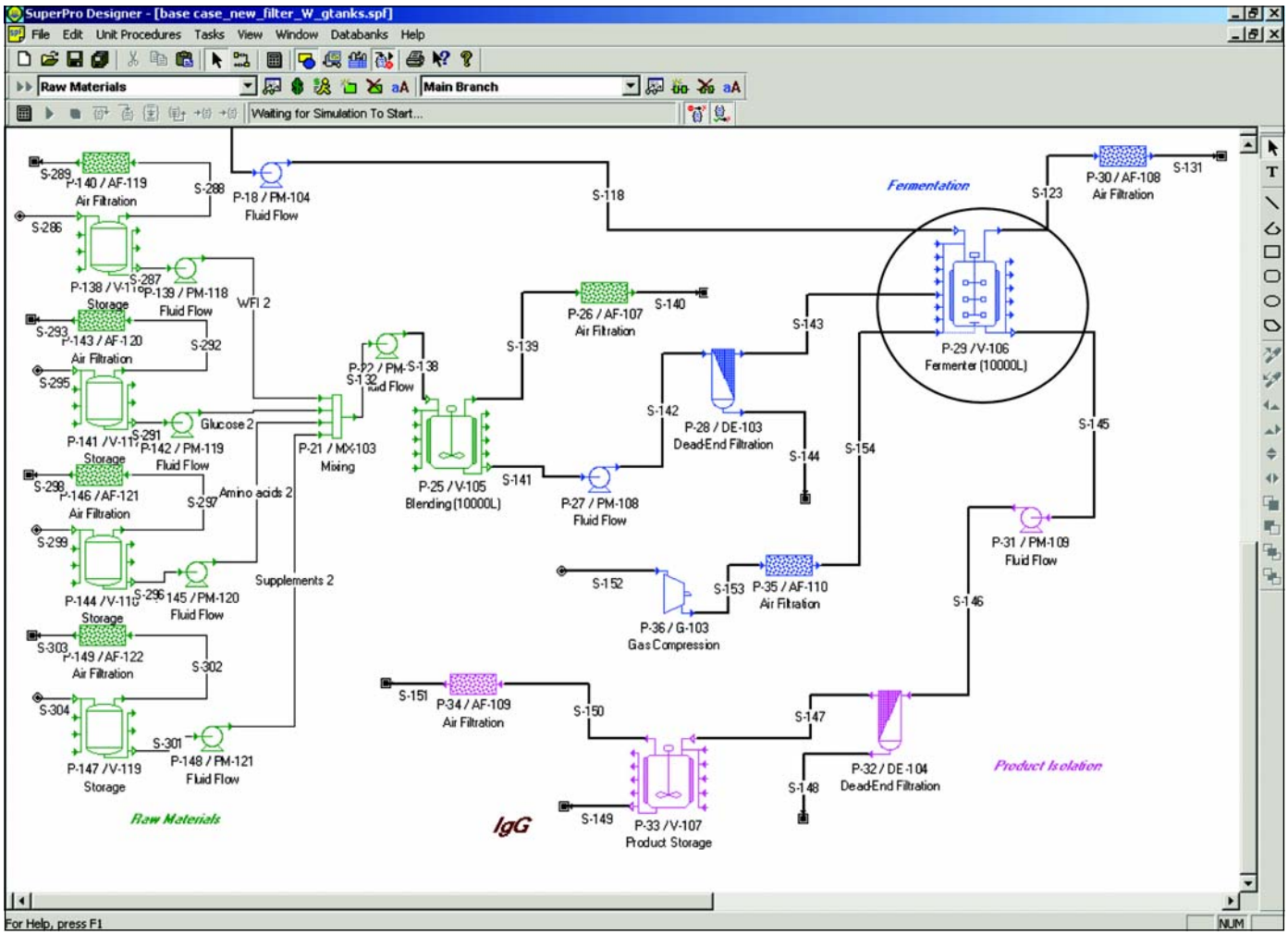

Figure 2. Excerpt of flow-sheet showing the 10,000L fermenter.

Item	Qty	$/unit	$/kg	$/kg	Reference*
Alanine	1 kg	$ 493.10			
Arginine	1 kg	$ 178.60			
Asparagine	1 kg	$ 237.60			
Aspartic acid	1 kg	$ 97.20			
Cystine	1 kg	$ 419.00			
Glutamic	1 kg	$ 53.00			
Glutamine	1 kg	$ 371.10			
Glycine	1 kg	$ 57.80			
Histidine	1 kg	$ 530.30			
Isoleucine	1 kg	$ 748.70			
Leucine	1 kg	$ 431.60			
Lysine	1 kg	$ 87.50			
Methionine	1 kg	$ 295.50			
Phenylalanine	1 kg	$ 233.30			
Proline	1 kg	$ 507.00			
Serine	1 kg	$ 525.00			
Threonine	1 kg	$ 895.50			
Tyrosine	1 kg	$ 308.80			
Valine	1 kg	$ 394.20			
Amino acids	**19 kg**	**$ 6,864.80**		**$ 361.31**	All on p. 425
Glucose	**1 kg**			**$ 20.60**	p. 485
Insulin	500 mg	$ 187.40	$ 374,800.00		
Transferrin	1 g	$ 458.40	$ 458,400.00		
2-mercaptoethanol	1 L	$ 71.90	$ 71.90		All on p. 956
Protease free BSA	100 g	$ 631.20	$ 6,312.00		p. 949
Ethanolamine	1 L	$ 26.70	$ 26.70		p. 966
Penicillin V	50 ml	$ 17.00	$ 340.00		p. 458
Supplements	**6 kg**		**$ 839,950.60**	**$ 139,991.77**	p. 486
WFI	**1 kg**			**$15.90**	p. 435

*Reference: Products for Life Science Research, Sigma 2003.

Table D. Raw Materials Purchase Cost.

(I/O) dialogs. In some cases, the default values recommended by the program were used for the simulation.[7] For example, the set up time for charging biomass into the 100L seed fermenter was set by default at 20 minutes - *Figure 3*. Similarly, the process time for charging the 100L seed fermenter was calculated from the default mass flow rate, which is set at 10 kg/min. These default values reflect typical operating conditions in the biochemical/pharmaceutical/waste treatment process industries.[7]

By analyzing the equipment utilization chart generated by the program, the 100L seed fermenter, 1,000L fermenter, and the 10,000L final fermenter were identified as bottlenecks. To debottleneck production, the installation of additional fermenters coupled with a staggered operation mode was considered. This is discussed in greater detail in the next section.

Equipment Utilization

One advantage of plant-wide simulations is the ability to identify potential bottlenecks and formulate strategies to increase throughput through debottlenecking. Various scenarios can be modeled to select the configuration that will give the best return on investments. We have identified a production bottleneck based on our simulations and proposed a strategy to increase throughput. Figure 4 shows the equipment utilization chart for the base case, where fermenters are operated in series. It is evident that the 10,000L fermenter (V-106) is the bottleneck in this case as the vessel is continuously utilized to process the batches produced by the smaller fermenters. Since the second batch cannot begin until the first batch is completed, the number of batches per campaign becomes solely dependent on the time taken to turnaround the 10,000L fermenter.

To debottleneck the process, additional fermenters were added and operated in stagger mode to increase the annual throughput - *Figure 5*. By adding two additional seed fermenters, one 1,000L fermenter and two 10,000L fermenters, the production schedule for each batch can be overlapped. After the first 100L seed fermenter starts for 72 hours, the second 100L fermenter begins, and after a lapse of 125 hours, the third seed fermenter commences. Staggering the operation of the fermenters in this manner reduced the effective batch time from the original 147 hours to 76 hours. Consequently, the number of batches increased from 51 to 102 annually. Annual production doubled from 134kg to 267kg of main product.

Economic Analysis

To evaluate the economic feasibility of the normal and staggered operation designs, indicative values for the cost and revenue streams were used. While these cost values may not be accurate in the absolute, they are very valuable in being able to compare different scenarios, and illustrate the usefulness of such process simulations for quickly estimating the economics of different design and/or operation options.

Purchase prices for the 100L, 1,000L, and 10,000L fermenter and blending tanks were indicative quotations from an established company. Equipment such as air filters and

dead end filters were considered as part of the fermenter package. Table D lists the purchase cost of raw materials obtained from the SIGMA catalog and Table E lists major equipment costs from an established bioreactor manufacturer. It is acknowledged that the retail price listed in the catalog is for laboratory-scale quantities and actual prices for plant scale quantities may be very different. In our design, the main revenue stream was calculated based on the flow rate of IgG in the revenue stream (S-149). The selling price of therapeutic proteins ranges from $5,000 per gram for Mabs to $1 million per gram for erythropoetin; we chose a selling price of $10,000 per gram for this simulation.

The simulator estimates the capital and operating costs, performs thorough cost analysis, preliminary economic evaluation, and profitability analysis. It provides information on fixed capital cost, operating cost, profitability, and cash flow analysis, which are needed for economic evaluation of greenfield projects.

Fixed capital investment was estimated based on total equipment cost and various multipliers. These multipliers are shown in Table F. All multipliers that affect the capital investment are section-specific and based on industry standards. In our base case, the Total Plant Direct Cost (TPDC) was calculated to be $33.9 million. This includes the equipment purchase cost, installation, process piping, instrumentation, insulation, electrical, buildings, yard improvement, and other auxiliary facilities. The Total Plant Indirect Cost (TPIC), which includes engineering, construction, contractor's fee, and contingency, was $28.5 million. The Direct Fixed Cost (DFC) for building the plant is the sum of TPDC and TPIC, a total of $62.4 million. Table F shows the summary of the fixed capital and the breakdown for building the production plant. The optimized case has more equipment, hence, the DFC increased from $62.4 million to $91.2 million, an approximate 1.5 fold increase.

Labor cost was estimated based on a unit-specific ratio of operator hours required for each hour of equipment operation. The unit labor costs of a process could be specified either as a lumped estimate or as an itemized estimate. We chose the itemized estimate of $57.5 per labor hour, calculated based on a formula in the software which incorporated factors for fringe benefits, supervision cost, operating supplies cost, and administration cost. In the design, labor cost was calculated for the different sections – raw materials, fermentation, and product isolation. Table G shows a summary of the labor requirement and cost for the optimized case. With an annual labor hour of 26 thousand hours, the labor cost for the raw materials section was $1.52 million – 31.9% of the labor costs.

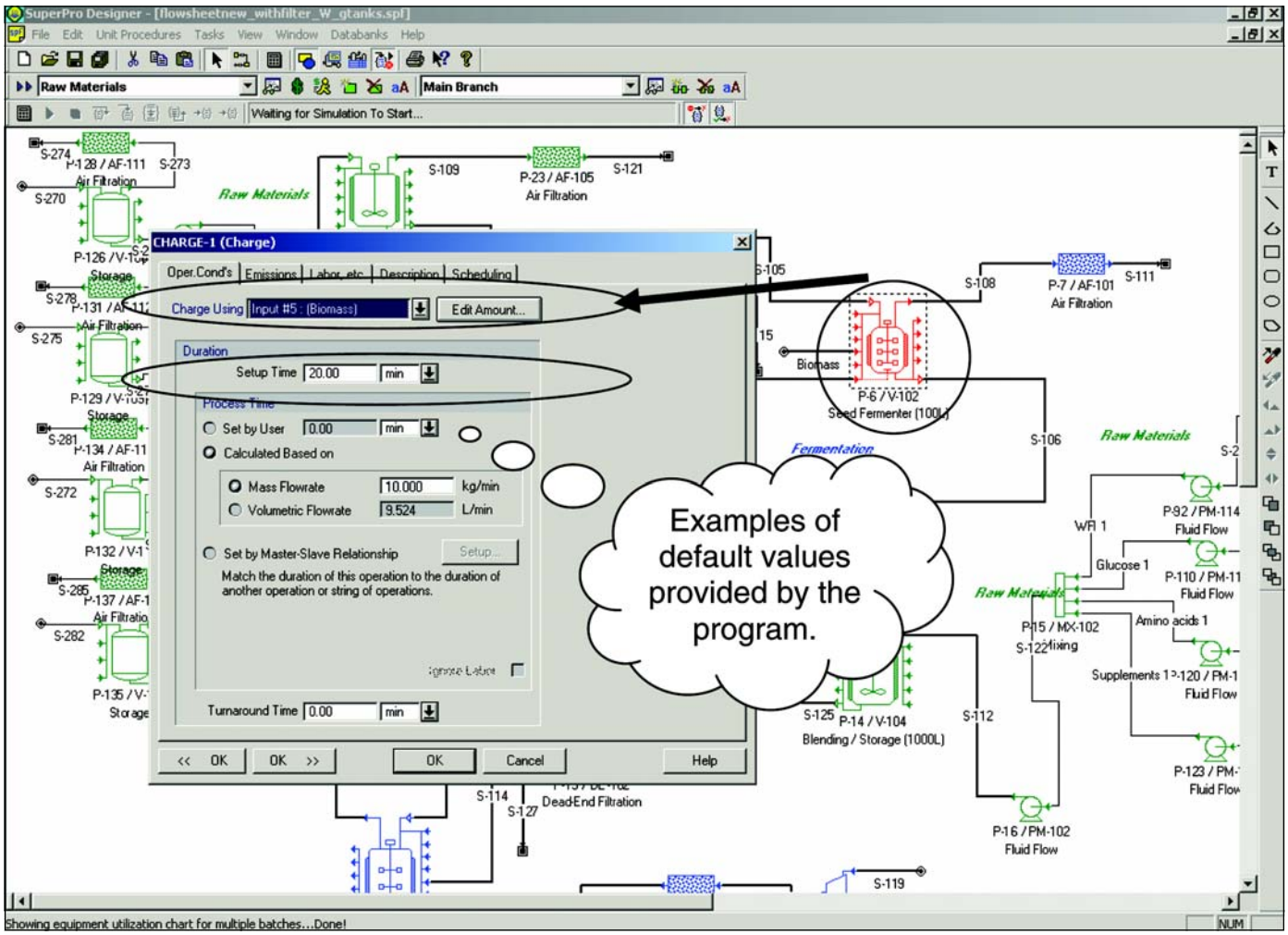

Figure 3. An example of preset default values in the I/O dialog for charging the 100L seed fermenter.

Equipment	Prices $'000	Reference
Fermenters		
100L	$ 400.00	From established company
1000L	$ 700.00	
10000L	$ 1,350.00	
Blending/Storage Tanks		
100L	$ 200.00	From established company
1000L	$ 350.00	
10000L	$ 500.00	

Table E. Equipment purchase cost.

The fraction was calculated based on the formula:

$$\text{Percentage of labor cost by specific sections} = \frac{\text{Labor cost } (\$ \text{ millions/year})}{\text{Total cost } (\$ \text{ millions/year})}$$

(Note: This included labor which is equipment dependent at $167 per equipment hour, and inclusive of lab/QC/QA)

The number of labor hours for the bioreactor section was 49 thousand hours. With labor rate set at $57.5/hour, this gave a labor cost of $2.82 million, which translated into 59.3% of the entire labor costs requirement. In addition, 7.3 thousand hours were needed for product isolation, resulting in a labor cost of $0.42 million. During the production phase, as more bioreactors operated in stagger mode came on stream, spikes in manpower needs occurred with a corresponding increase in labor cost in the bioreactor section.

Nutritive raw materials, priced at $360 per kg of amino acid and $20 per kg of glucose, summed up to an annual amount of $0.73 million and $0.11 million, respectively. The remaining cost was contributed by supplements, WFI, and water for washing. Table H is a summary of the raw material costs. The largest proportion of cost comes from the water for equipment cleaning. Compared to the values from the un-optimized base case, the requirements and costs for the de-bottlenecked scenario was almost double for each individual component, but remained in the same proportion.

The operating cost calculations were then calculated around process sections. All multipliers that affected the operating cost are section-specific. Table I gives a summary of the annual operating cost and breakdown. The equipment dependent cost accounted for depreciation, maintenance, and equipment expenses. This formed the largest cost after raw materials.

The annual operating cost, based on 2002 prices, is $147.23 million for the optimized case and $78.19 million for the base case. This amount was contributed by the costs of raw materials, labor and equipment dependent costs, the costs incurred in laboratory work/QC/QA (0.15 of the labor-dependent cost in our design case, but could be set at three times the labor cost), consumables (e.g., replacement of membranes and resins, set at 0.025 of the labor dependent cost), and utilities, such as heating and cooling of process streams, which is set at 0.08 of the labor-dependent cost. In our design, the bulk of the annual operating cost was due to raw materials. For the optimized case, this amounted to about $125.73 million, 85% of the total operating cost. For the base case, this value was $62.86 million, approximately half the amount of the optimized case.

Table J shows the profitability analysis for the production plant. With a direct fixed capital of $91.16 million and estimated start-up cost of $201 million,[8] the production unit cost per kilogram of IgG was $0.55 million with an annual production of 267.17 kg of main product. Upfront R&D was assumed to be a conservative value of $0.5 million. Upfront royalties were not considered because we have assumed that the manufacturing company developed both the cell line and antibody. With a conservative selling price of $10 million/kg of Mab,[9] the annual revenues would be $2.67 billion. Gross

		$ millions			
		Base Case		Optimized Case	
Capital Cost					
Equipment Purchase Cost					
Direct Fixed capital (DFC)					
Total Plant Direct Cost (TPDC)					
Equipment Purchase	PC	10.25		15.50	
Installation	0.4 × PC/0.29 × PC	4.39		4.91	
Process Piping	0.35 × PC	3.59		5.42	
Instrumentation	0.4 × PC	4.10		6.20	
Insulation	0.03 × PC	0.31		0.47	
Electrical	0.1 × PC	1.03		1.55	
Buildings	0.45 × PC	4.61		6.97	
Yard Improvements	0.15 × PC	1.54		2.32	
Auxiliary Facilities	0.4 × PC	4.10		6.20	
TPDC			**33.90**		**49.54**
Total Plant Indirect Cost					
Indirect Cost (IC)					
Engineering	0.25 × DC	8.47		12.39	
Construction	0.35 × DC	11.86		17.34	
Contractor's Fee	0.05 × (DC+IC)	2.71		3.96	
Contingency	0.1 × (DC+IC)	5.42		7.93	
TPIC			**28.46**		**41.62**
DFC = (TPDC + TPIC)			**62.36**		**91.16**

Table F. Capital costs and the respective multipliers.

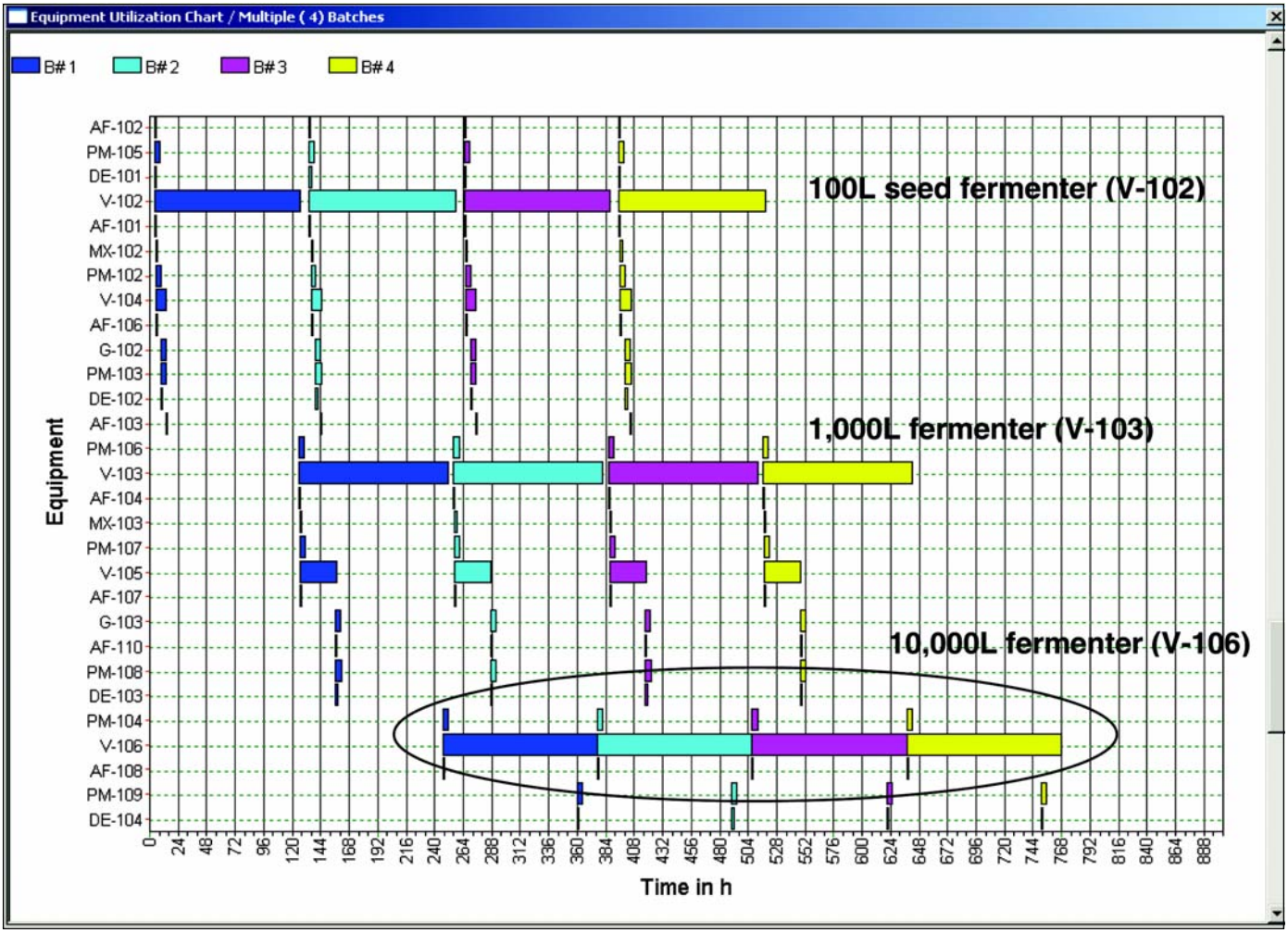

Figure 4. Equipment utilization chart (Base case).

profit would then be $2.52 billion, which is the difference between the annual operating cost and revenues. The net profit after 40% tax based on US rates and depreciation would hence be $1.52 billion. Gross margin was hence 94.49% with a Return On Investment (ROI) of 504.3% and a payback time of 0.2 years. For the base case, the gross margin is similar, but ROI is lower (283.04%), and payback time is longer (0.35 years).

While our simulation was based on a batch production of antibodies, it should be possible to simulate a fed-batch or perfusion culture (which are more productive) in future versions of commercial simulation software. However, the appropriate material balances will have to be determined. In our experience, there is great flexibility in being able to specify equipment, consumables, and labor costs allowing multiple scenarios unique to antibody manufacturing companies that could be generated and evaluated.

Discussion

The increased demand for monoclonal antibodies is contributed by their increased application as human therapeutics. Moreover, the dosage per patient for Mabs is relatively high compared to other glycoproteins, for example, up to 1 g/dose of Rituxan or Remicade Mabs are required for adults and multiple doses may be given. However, currently there is a worldwide shortage of mammalian cell bioreactor capacity required to satisfy this high demand.[10] In order to improve production, several strategies have been attempted. Highly expressing cell lines with enhanced productivity have been created. Extended culture longevity and maintenance of high specific secretion rates have been achieved through genetic engineering techniques.[11] Physicochemical parameters such as culture pH, temperature, and dissolved oxygen levels also have been optimized in the bioreactor. To maintain a conducive nutritional environment, commercial processes are typically operated in fed-batch mode. The supply of nutrients, minimization of waste product and environmental conditions has been manipulated for the optimal design of fed-batch processes.[12-14] However, even with these improvements, biomanufacturers may still be unable to satisfy the high volu-

Section Name	Labor Hours per Year (thousands)	Labor Cost $/year (millions)	%
Raw Materials	26.3	1.52	31.9
Fermentation	49.0	2.82	59.3
Product Isolation	7.3	0.42	8.8
Total	82.6	4.75	100

Table G. Summary for labor requirement and cost summary for optimized case.

Raw Materials	Unit Cost ($/kg)	Base Case		Optimized Case	
		Annual Amount (000 kg)	Cost ($mil/yr)	Annual Amount (000 kg)	Cost ($mil/yr)
WFI	15	3422.20	51.33	6844.40	102.67
Glucose	20	2.64	0.05	5.28	0.11
Amino Acids	360	1.01	0.36	2.03	0.73
Supplements	139,992	0.08	11.03	0.16	22.06
Water	0.023	3544.30	0.08	7088.60	0.16
Total	**140,387**	**6970.23**	**62.86**	**13940.47**	**125.73**

Table H. Raw materials cost summary.

Cost	Base Case		Optimized Case	
	$ millions/yr	%	$ millions/yr	%
Raw Materials	62.86	80.39	125.73	85.39
Labor-Dependent	2.37	3.04	4.75	3.23
Equipment-Dependent	11.74	15.01	14.32	9.72
Laboratory/QC/QA	0.36	0.46	0.71	0.48
Consumables	0.72	0.93	1.45	0.98
Utilities	0.14	0.18	0.28	0.19
Total	**78.19**	**100**	**147.23**	**100**

Table I. Summary for annual operating cost.

metric demand for Mab products. Plant-wide process optimization may help to further improve the overall plant output. Conventional pilot plant experiments are costly and time consuming. On the other hand, process simulations can be used to minimize the number of pilot plant experiments required. Combining these two approaches will help to identify potential constraints and problems faced by plant operations at an early stage. These problems can then be resolved before the plant is built.

To determine the stoichiometric coefficients and other process inputs required for the simulation, only simple laboratory experiments are needed. In our design case, we grew our cell cultures in shake flasks and assumed that data obtained in shake flasks was representative of large-scale bioreactors. However, controlled conditions in bioreactors may provide significantly better yields.

Plant-wide simulations can facilitate process optimization efforts. As illustrated in this study, production bottlenecks can be easily identified. The example presented in this article showed an annual production increase from 134 kg/year to 267 kg/year by increasing the number of bioreactors and staggering their operation times. Although the operation and equipment cost was higher in the optimized case, the increase in revenue resulted in an overall increase in net profits. As increased yield or product recovery is often only achieved at the expense of higher cost of equipment, operation, or raw materials, plant-wide simulations would be very useful for assessing the overall economic impact of various process optimization initiatives.

Another scenario that may be modeled is a change in vessel size. This can impact the equipment cost, as well as the cost of construction and maintenance. Other possible scenarios include changes in the labor costing structure, or variations in market demand and product pricing. By modifying the process flow sheet or input variables, various scenarios can be easily modeled and compared. Although these were not performed, we can anticipate that such simulations will be useful for cost evaluations.

In order to generate realistic cost estimates, raw material costs should ideally be obtained from potential suppliers of bulk materials. In our case, we collected these data from a commercial catalog -*Table D.* Although the costs are relatively high, there should be economy of scale with bulk purchase. Apart from raw material costs, the costs for vessels, equipment, production buildings, storage facilities, laboratories, offices, utilities, and other facilities also should be considered during the economic analysis of the plant design. In our design, the start-up and validation cost of $200 million was based on an estimated value from the capital cost to produce biopharmaceuticals.[8] Upfront R&D was estimated to be a conservative sum of $0.5 million. Royalties and license fees also would be payable if the cell line and antibody has not been developed by the operating company. However, these may be paid as a lump sum, included in the fixed capital or as an annual fee. Payments also could be based on a percentage of the amount of product sold, which could reduce the net profit substantially. Taxes and labor costs also differ for different countries. For example, the taxes in Singapore are lower (24%) compared to the US (40%), resulting in higher returns.

The payback period of 0.2 years in the model presented here appears to be quite short. However, it should be noted that the simulation model assumes that the plant is able to run at full capacity when the equipment is installed. In practice, a substantial amount of time may be required to test and validate the equipment and process before the plant can be fully operational. Furthermore, the present model focuses only on the upstream portion of the plant. The final full model, which includes the downstream portion of the plant, will have a higher total fixed cost and start-up cost. Some antibody also may be lost in the downstream purification

process. These combined effects may reduce the net profit and hence lengthen the payback period.

The software is relatively easy to use and result outputs are generated almost instantaneously. Previous publications[15, 16] have used Aspen Batch Plus and compared it to earlier versions of Superpro for the modeling of vaccine and tissue plasminogen activator (tPA) production respectively. In the former, a variety of processes were simulated and in the latter case, tPA production capacity of 11kg/annum was modeled. They conclude that both are equally suitable for economic modeling, but both have shortcomings in predictive models for biochemical unit operations.

Conclusions

We have demonstrated a simple approach to increase Mab production throughput by staggering bioreactor operation and provided a detailed simulation of a plant producing multi-kilogram quantities of Mabs. The model was constructed in Superpro 4.9 software based on measurements from cell culture experimental runs and economic data from various sources. Using plant-wide simulations like this can facilitate the planning process through systematic and comprehensive consideration of the large number of factors involved. Furthermore, by making modifications to this basic model, different scenarios may be simulated to study their impact on production and profitability.

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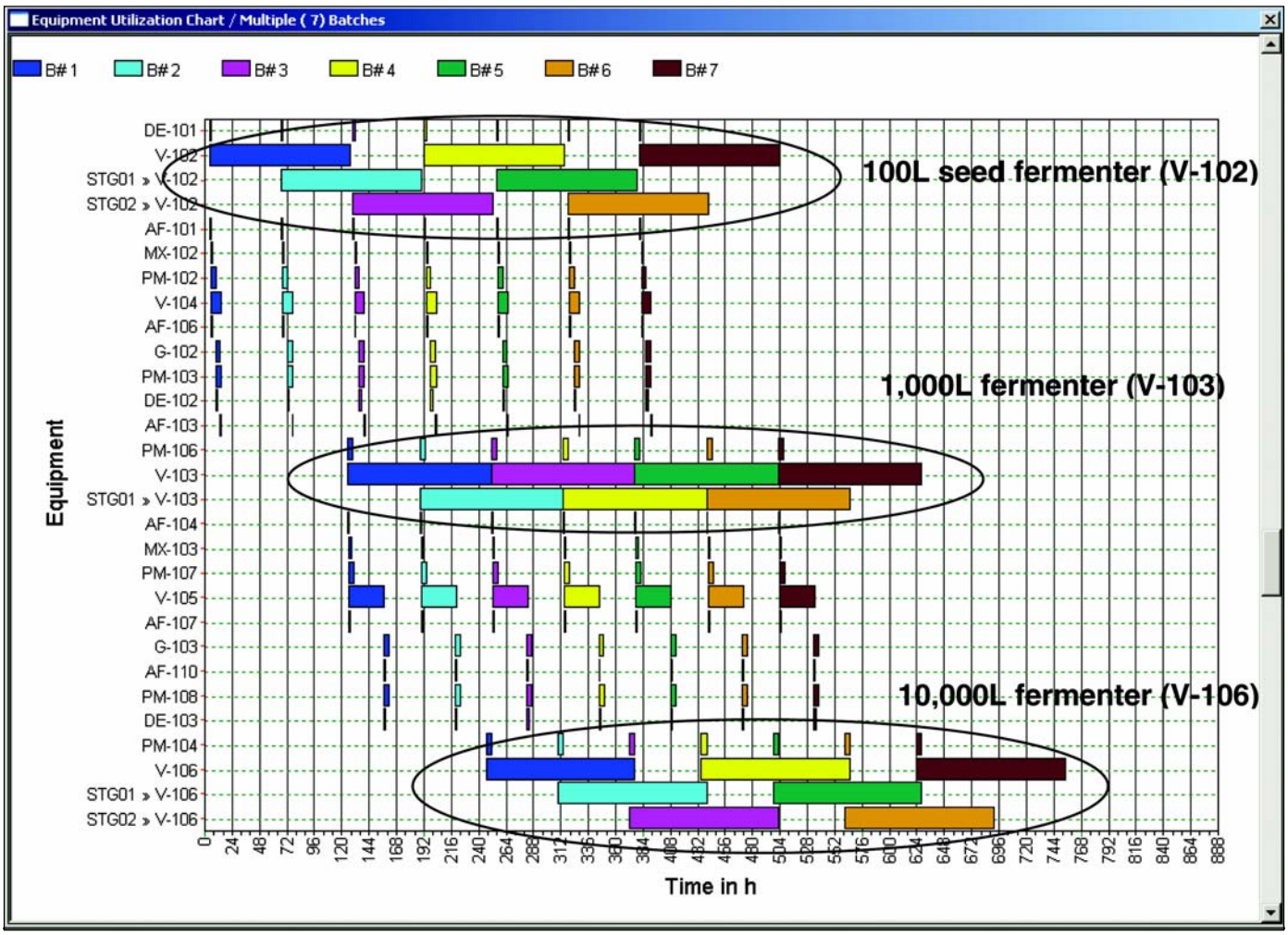

Figure 5. Equipment utilization chart (Optimized case).

	$millions	
	Base Case	**Optimized Case**
A. Direct Fixed Capital	62.37	91.16
B. Working Capital	4.59	8.61
C. Start-up Cost	201.23	201.23
D. Up-front R&D	0.50	0.50
E. Up-front Royalties	0.00	0.00
F. Total Investment (A+B+C+D+E)	268.69	301.50
G. Investment Charged to Project	268.69	301.50
H. Revenue Stream Flow-rates [kg/year of IgG (in S-149)]	133.59 kg/year	267.17 kg/year
I. Production Unit Cost [$millions/kg of IgG (in S-149)]	0.59	0.55
J. Selling/Processing Price [$millions/kg of IgG (in S-149)]	10.00	10.00
K. Revenues ($millions/year)	1,335.86	2,671.72
L. Annual Operating Cost	78.19	147.23
M. Gross Profit (K-L)	1,257.67	2,524.49
N. Taxes (40%)	503.07	1,009.79
O. Net Profit (M-N+Depreciation)	760.53	1,520.48
Gross Margin	**94.15%**	**94.49%**
Return on Investment	**283.04%**	**504.31%**
Payback Time (years)	**0.35**	**0.20**

where,

$$\text{Gross Margin} = \frac{\text{Gross Profit}}{\text{Revenues}}$$

$$\text{Return on Investment (ROI)} = \frac{\text{Net Profit}}{\text{Total Investment}} * 100\%$$

$$\text{Payback Time (in years)} = \frac{\text{Total Investment}}{\text{Net Profit/Year}}$$

Table J. Profitability analysis.

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Concludes on page 60.

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How Object-Oriented Design Can Drive Down the Cost of Implementing and Validating Automated Processes

by Phillip Maderia

This article presents a software design methodology that reduces the time it takes to develop, test, and document application software and enables testing to occur before the automation is installed.

A major contributor to the high cost and extended schedules experienced when bringing new manufacturing capacity on stream in FDA-regulated industries is the need for computer systems validation. The traditional approach to automation software validation requires the development, review, approval, execution, and documentation of large numbers of test protocols. The effort is typically done *after* the automation is installed which puts the computer system validation on the critical path for starting up the process.

Genzyme has developed a strategic approach toward automation software design that can substantially cut the cost and schedule for automation projects. The software design methodology described in this article reduces the time it takes to develop, test, and document application software and enables testing to occur *before* the automation is installed, which substantially reduces the computer systems validation work that is on the project critical path. The approach is based on the use of standards, software encapsulation, and self-documenting control modules. The approach to cost savings associated with computer systems validation for process automation documented in this article can only be attained if an organization adopts a strategic approach across multiple projects. The benefits that can be attained are very substantial; however, organizational commitment, procedure development, and standards are required. The components of our strategic approach to automation are:

- Standardized Documentation
- Standards Library
- Using Object-Oriented Software Design
- Self Documenting Control Modules
- Operational Qualification (OQ) Protocol Standard Operating Procedure (SOP)

Time and labor savings are seen because:

- Control modules are tested once. The same control module may be used many times within a project and on multiple projects, but are only tested once.
- Control module software is highly leveraged within a project and between projects.
- Procedure, operation, and phase level testing is accomplished using an OQ protocol standard operating procedure, substantially reducing the time required to develop, review, and approve the test protocols

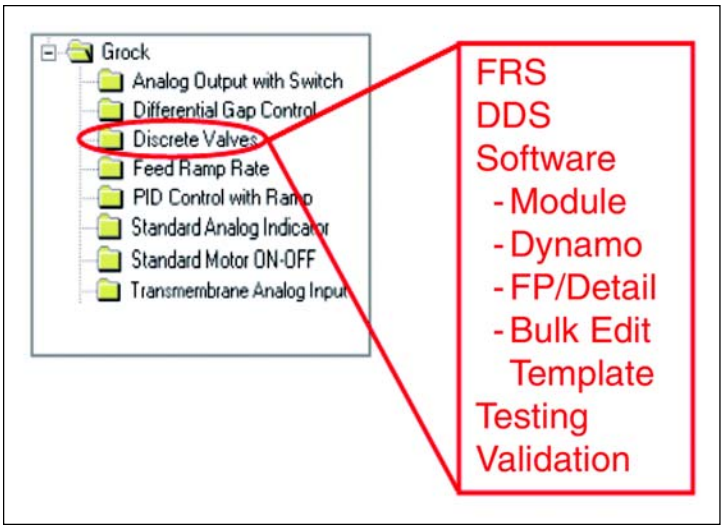

Figure 1. Genzyme Repository of Control Knowledge (GROCK) Content.

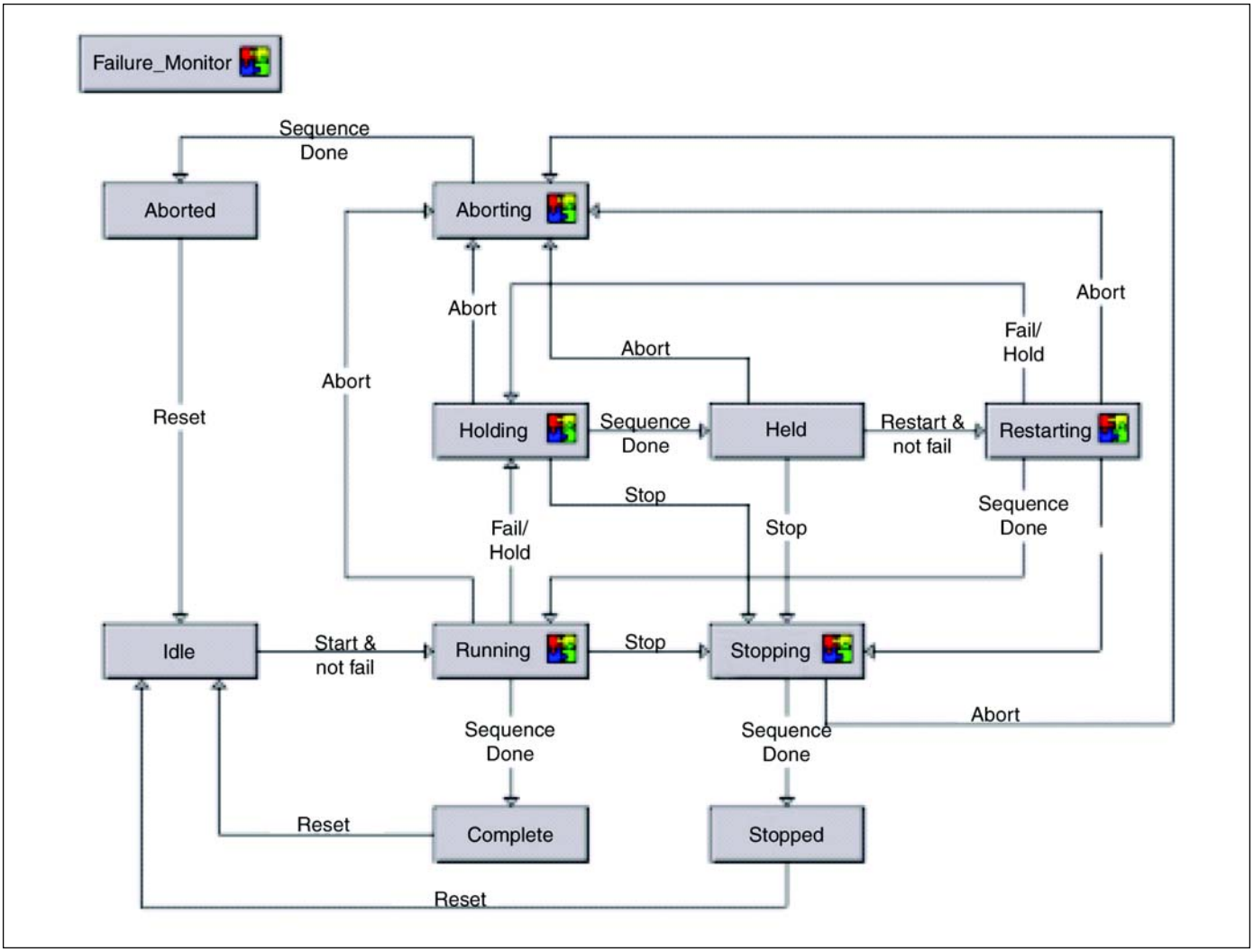

Figure 2. State transition diagram.[2]

- Self documenting control modules are designed to generate documentation as the phase executes, making it much easier to verify that the procedures, operations, and phases actually performed to requirements of the test protocol and Functional Requirements Specification (FRS).

This article will review Genzyme's approach to automation and validation that enables these benefits to be realized.

Biotech is Well Suited for a Standardized Approach to Automation

In biotech recombinant DNA facilities, unit operations are very similar including media feed and preparation, buffer preparation and hold, cell culture, harvesting, micro-filtration, centrifugation, and chromatography. The hardware, skids, piping, and control strategies are therefore very similar. The similarity between biotech facilities is the primary reason why it is possible to use standardization to drive down the cost and schedule of automation. Over a series of projects, Genzyme sought to take advantage of the similarity in the biotech facilities to drive down costs and reduce the schedule for automation.

Strategic Approach to Automation

The first cell culture manufacturing plant built by Genzyme was the Allston Landing facility in Allston, Massachusetts, USA. This project started in 1992. This project, like many others at the time, was completed before Good Automated Manufacturing Practices (GAMP) and other automation standards were widely accepted. This resulted in several lessons learned; one of which being the development of automation design documentation.

The software design specifications for the project included both functional and design details. Therefore, each specification included too much programming information, did not distinguish between functional requirements and implementation details, and made it difficult to separate information from which to conduct structural and functional testing. After the Suite 1 project was successfully completed, we concluded that we could improve the way we manage automation projects, reduce the cost and schedule for automation, and ultimately improve the quality and long term maintainability of our automation systems.

Several years later, Genzyme planned a series of expansion projects including a new Suite 2 in the Allston facility, future Suite 1 migration from RS3, system upgrade in

Framingham, and the construction of a new state of the art facility in Belgium. Having a series of projects presented the opportunity to redesign the way we did automation and deliver savings. We began this process by first setting out the goals for our automation strategy. These included:

- developing a new model for functional requirements specifications
- leveraging control knowledge
- standardizing on control designs
- reducing the amount of non-value added testing
- increasing the efficiency of the test procedures

Functional Requirements Specifications

The first thing we did was redesign our approach to specifications. We replaced the highly detailed Implementation Specification with a separate Functional Requirements Specification (FRS) and a Detailed Design Specification (DDS) per the GAMP guidelines. The FRS document was designed with the following three priorities in mind:

Priority 1: Manufacturing

The FRS document's first priority is for the manufacturing personnel to understand how to operate the process with the automation system.

Priority 2: Validation

The FRS document's second priority is to facilitate the writing of test protocols by validation personnel to verify the functionality of the automated system.

Priority 3: Automation

The last priority of the FRS document is to serve as the requirements document from which the detailed design documentation for the automation system is developed. Care is taken in the DDS document to define the next level of detail without duplicating the contents of the FRS.

Standards Library

Re-using work from one project to the next is the single largest opportunity to drive down the cost of automation. It is generally accepted that hardware and system software costs are less than 25% of the overall cost of an automation project in the biotech industry. The remaining 75% comes from engineering, testing, and documentation. Leveraging work from one project to the next does not happen by accident. It

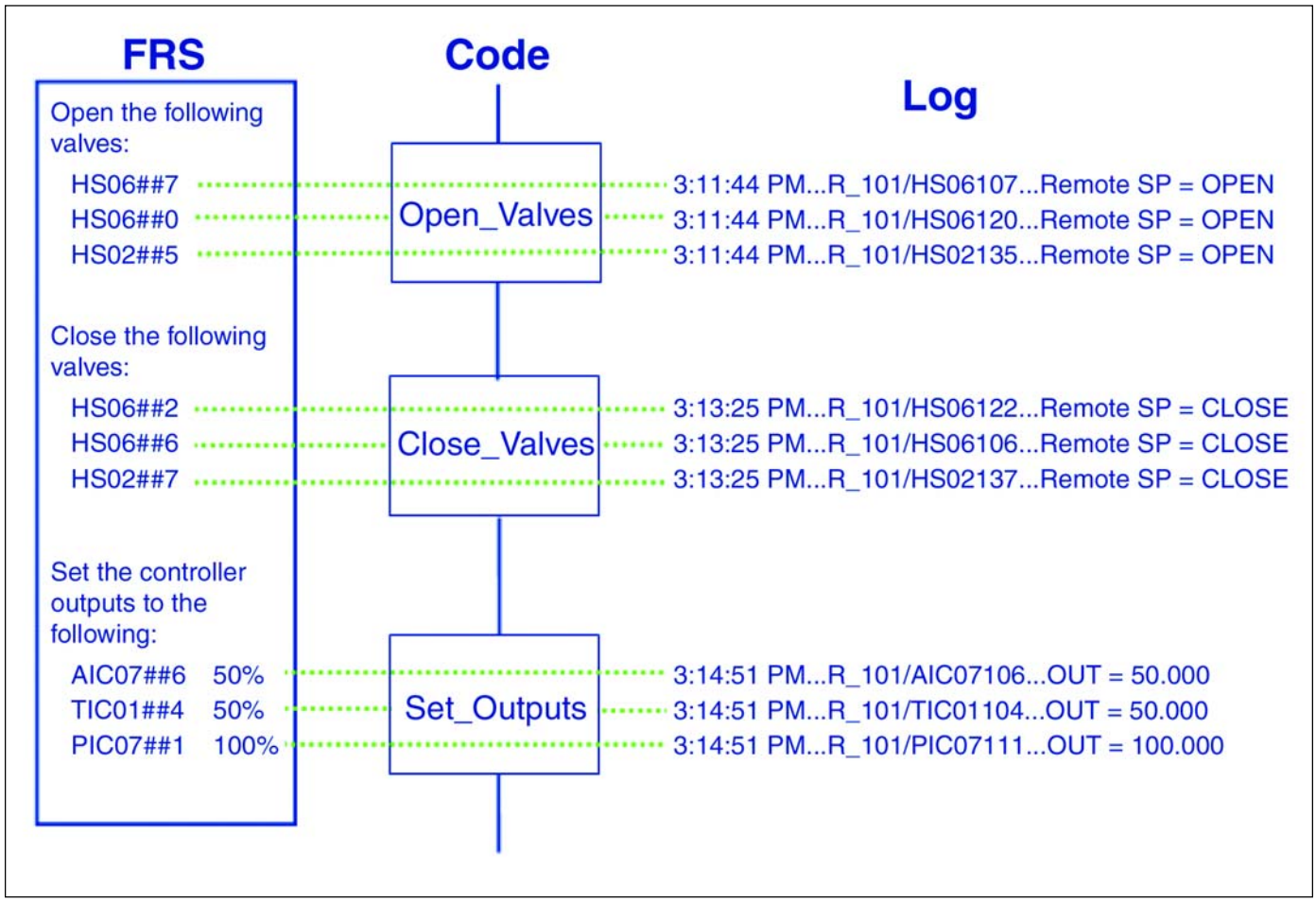

Figure 3. Design strategy.

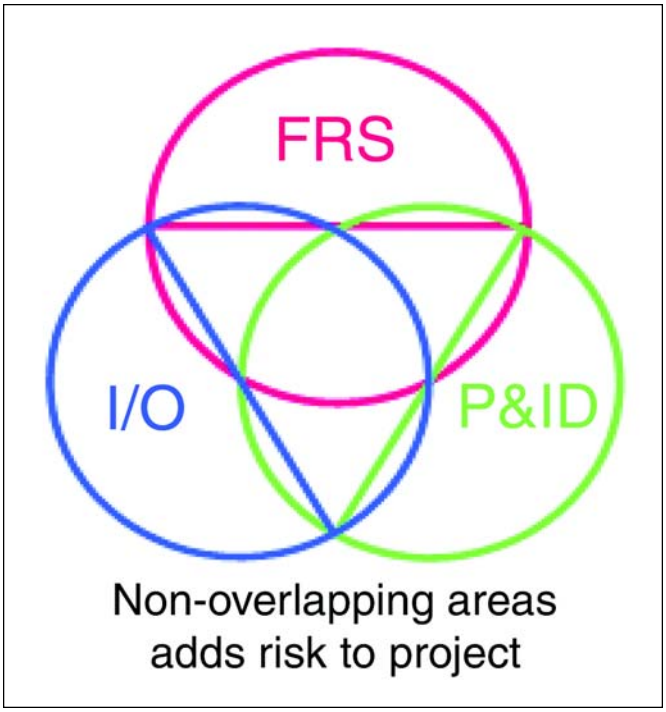

Figure 4. Non-matching feed documentation.[3]

requires an investment in organization and work process.

A key to achieving our goal to leverage work between projects is the use of object-oriented system configuration software to create a series of unique, validated control modules. Each module – "shrink-wrapped" together with its design documentation, test protocols, and validation test documentation—is saved as a member of a library of control modules. At Genzyme, we have formally established the **Genzyme Repository of Control Knowledge (GROCK)** as the Genzyme Therapeutics Manufacturing and Development library to maintain control modules including FRS, DDS, graphic display components, test protocols, and test documentation - *Figure 1*.

Since the library is object oriented and each instance of a module is identical to the parent module, the library is leveraged across the organization to configure any number of automation projects without the need of testing every instance of the control module within a project or retesting the module when used in a different project.

Maintaining the complete design and testing documentation for the modules in the library and using procedures that provide project traceability to the library avoids the requirement to re-develop module level documentation and testing. The goal was to be able to assemble control systems software like Legos™ from pre-validated control modules. The cost associated with the first project is relatively high compared to subsequent projects because of the need to initially develop control modules, documentation, and testing in a way that would be adaptable and traceable.

Strategic Management is Essential

Most organizations do not treat automation as a strategic asset; so often, each project is executed differently. Different technology may be selected, different integrator organizations may be used, and control modules are developed, documented, and tested with limited regard to what has been done in the past. Design and development are normally outsourced to system integrators on a competitive bid basis. The integrator may focus only on cost and schedule using their company standard work processes. In a competitive situation, you can not rely on a contractor to focus on the big picture of implementing work methods that reduce costs and schedules for a series of projects over a period of years. Cost reductions that can be accrued by the use of standards can only be realized when the end user company has made a commitment to drive down costs over several projects. This requires a sustained program supported by management with the full involvement of production, engineering, and validation.

In addition, system integrators should be selected and made partners that understand and share in the standards, work methods, and goals to drive down costs. With a partnership, a vision for automation can be developed in a win/win fashion. To date, that strategy has paid large dividends to Genzyme and its partners.

Not Just Copy and Paste

Leveraging existing control modules from one project to another is common through copying control modules. But reducing control module documentation and testing can only be accomplished in a regulatory compliant fashion with a program in place that manages both the application code and the documentation such that it is fully traceable to previously tested code. This should include Standard Operating Procedures (SOPs) that describe how software is maintained in a library and how a project should access and use modules from the library such that traceability to tested code is maintained. The Validation Master Plan (VMP) and Quality Project Plan (QPP) should specifically address the process of

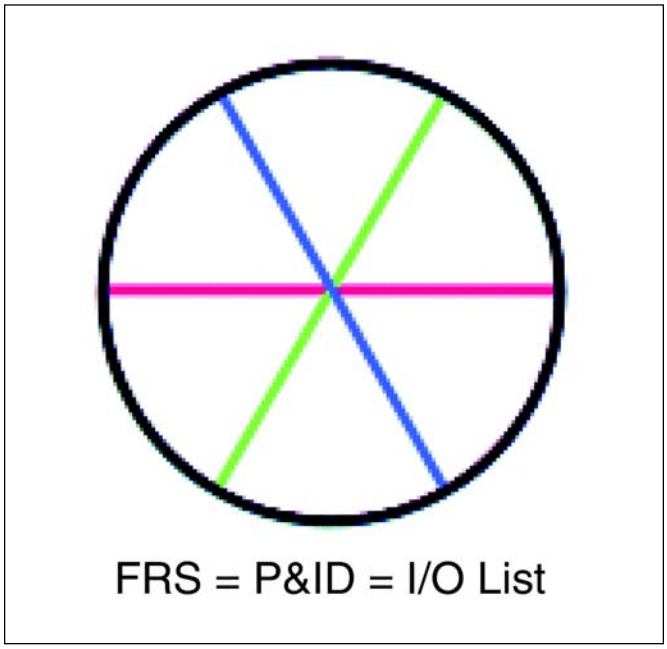

Figure 5. Matching feed documents.[3]

leveraging existing control modules and identify how much additional testing should be done when control modules are re-used within a project and between projects.

When managing a control modules library it needs to be recognized that new projects may require the development of control modules that do not exist in the library. It will be necessary to have a procedure in place to manage the need for new modules. In addition, control modules never change once they are implemented on the first project. If there is value in adding new functionality into an existing module, a new module, containing the new and old functionality (in part or in whole) must be built from scratch, tested, validated, and added into the library. The new module is then available to all previously executed projects. Provided that there is justification to do so, each prior project can migrate from the old module to the new one at the project team's discretion. Once all projects have migrated to the new module, the old module can be retired and all subsequent projects will use the new module.

Training is essential for the team members to manage the use of a control module library on a project and between projects. Genzyme has developed control module training for the software development team. A specific Web-based training module is developed for each type of control module; a total of 31 training modules have been built to date. As engineers are brought onto the different Genzyme projects, they are required to go through each training module. This process helps ensure that new engineers continue to maintain the consistency established with the module library.

Object-Oriented Design and Implementation

Many may shudder at the idea of not executing detailed test protocols on every instance of a control module. Since every control module controls different equipment, how is it possible to not test every single instance of the control module?

The answer to this is the use of object-oriented design software implementation. As Genzyme moved forward with Suite 2 and the other projects, a control system was selected which supported object-oriented control module design. Object-oriented design allows the development of a 'module class' and uses the module class to create specific module "instances" of the module class. There is a profound difference between creating many different control modules by copying software compared with using object oriented software to create a module instance from a module class. A module instance is much like calling a subroutine (module class). This guarantees the software actually executing for each module instance is the same. This is not true with control modules that are created from copying control module code since there is no way to be sure other changes were not made after the code was copied. So the nature of object oriented control module design allows the module class to be developed and rigorously tested and all instances of that control module are assured to be identical to the module class with the exception of the specific tags they reference. Therefore, the only thing that has to be tested for all control modules is the correctness of the tag it references which is accomplished during structural testing and system Installation Qualification (IQ). The goal of using object oriented designs is to reduce the number of software modules that need to be designed, developed, documented, and tested.

Absolutely Generic

In order to make object-oriented design successful, module classes must be designed to be generic. Once logic is required that is equipment specific, then the idea of using module classes and module instances to reduce cost and schedule is lost. Exception handling makes it very challenging to write generic module classes. The S88 Phase state transition model (Figure 2) calls for six different transition states to contain logic. These are the 'Running' state that defines how the unit should run during normal conditions and the 'Holding,' 'Stopping,' 'Aborting,' 'Restarting,' and 'Failure Monitor' states that define how the unit should run during abnormal conditions. Typically, the logic in each of these states must be uniquely developed, documented, and tested from phase to phase. In order to take advantage of module classes and module instances to drive down to cost of automation, the logic in all these states must be the same. For example, a 'fill tank' phase may be logically identical from one tank to another, the logic required to handle abnormal conditions may be different from one tank to another or may be different even on the same tank depending where the process is at the time. Since the 'HOLD' logic is typically 30-50% of the code that needs to be configured, differences in abnormal condition logic or 'exception handling' is a real barrier to using common objects to reduce software development and testing.

In order to resolve this challenge, a technique was developed to make the abnormal condition logic identical in all instances. In order to achieve generic abnormal condition logic across all phases, we added 'exception handling' logic to all control modules in the GROCK library. Each module contains monitoring and failure positioning functionality.

A specific device module is requested to be monitored by the phase logic. If the device fails or goes into critical alarm, it passes its tagname up to the unit and the cause of the failure i.e., high temperature alarm. This functionality works in conjunction with the Fail Monitor in each phase.

Each module also has a failure position used when the phase goes to the HOLD state. For example, the phase will set a failure position of CLOSED for a valve as part of the normal RUN logic. If the phase goes to HOLD, the valve control module will store its current state and will then go to its failure position. The valve will return to its pre-HOLD state once the phase is restarted. This functionality works in conjunction with the HOLD and ABORT states in each phase.

Since this functionality is documented and tested within each control module, virtually no additional programming is required to handle exceptions at the phase level. This dramatically decreases the amount of documentation, programming, and testing typically required for abnormal conditions. In addition, smaller more reusable phases can be developed within the unit class which further reduces the amount of documentation, programming, and testing.

Validation Logging

While the methods described previously greatly reduce testing at the phase level, the actual manufacturing process is created by orchestrating the actions of many different control modules together to control an entire process. Using object oriented module design and leveraging pre-validated control module libraries cannot reduce the need to verify that all the control modules have been correctly applied in the right order with the right parameters to correctly execute the batch recipe. In S88 language, it is still necessary to test at the procedure, unit procedure, operation, and phase level.

The process of executing test protocols and verifying the control system is properly executing the functions called out for in the project FRS can be difficult and time consuming. The typical method of doing this would be to write a test protocol based on the FRS and the person executing the test protocol to sit at a workstation and verify that all phase logic executed as specified (IE, the proper valves opened and closed). At Genzyme, we have implemented the concept of Validation Logging into each GROCK control module to reduce the cost and time required to verify the performance of the batch software. Validation Logging is where the control module itself writes to the event log all actions executed by the control module. When a valve opens, this is logged. When a setpoint changes, this is logged. Modern control systems allow the application programmer flexibility to write free form messages to the logger. Using this capability, all control modules are written such that they log their actions to the event chronicle - *Figure 3*. Since these logged actions come directly from the module and not the phase logic, this makes the process of verifying the control system properly executed the phase requirements in the FRS much easier. The Operation Qualification (OQ) protocol simply verifies the steps in the FRS were in fact executed and this is verified by comparing the validation log to the action as called out for in the FRS. By planning to do this ahead of time, a tight correlation is built into the FRS and validation log so that the formats and wording make correlating these two documents easy.

This has several benefits. First, labor hours are reduced since a validation person does not need to be present while the code executes. Second, protocols can be written in reference to a test protocol SOP. For example, the test protocol would simply capture the FRS being tested, the phase version information, and the proper approvals and direct the tester to use the protocol SOP which governs the comparison of the FRS with the validation log. To test all phases, Validation Logging is turned on for the unit being tested and the procedure is run real time from start to finish. The validation log, filtered by the Batch ID, is then printed out and verified against the unit FRS. The FRS and the log are verified and signed off. Third, (and arguably most important), the validation log concept allows software to be tested to determine if it is executing unspecified actions. Normal test protocols can only test to verify if software performs the specified functions.

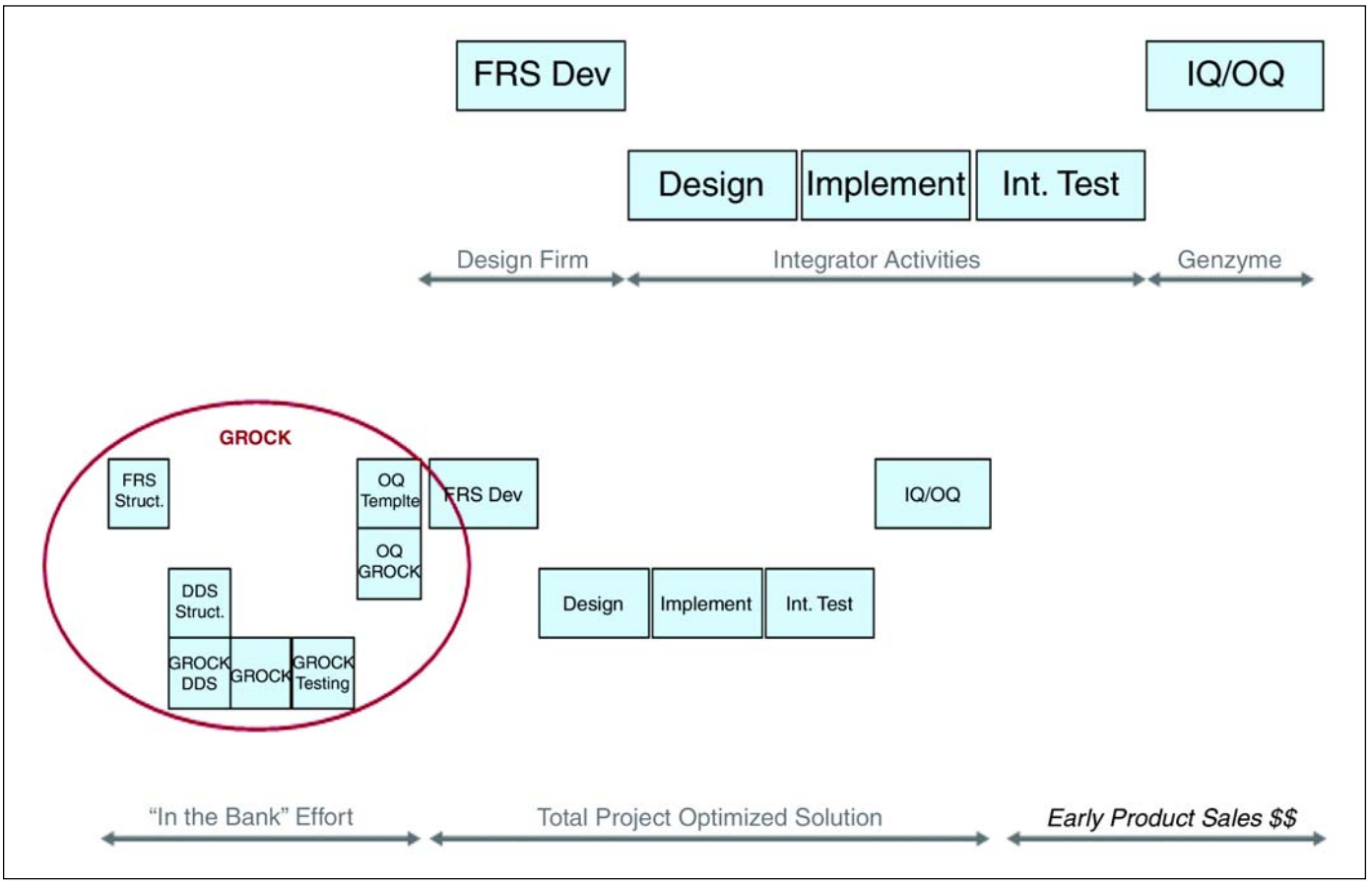

Figure 6. Total Project Optimized Solution.[3]

Unspecified Functionality

Test protocols normally do a poor job in determining if software performs unexpected functions. For example, if a phase was specified to open valves A, B, and C; a test protocol would be written to verify the phase opened valves A, B, and C. So long as valves A, B, and C were opened, the test would pass. What happens if the phase also opened valve X when it was not supposed to? Normally, the test would pass and valve X opening when it was not supposed to would go undetected until it was discovered at runtime by a plant operator or potentially during an investigation resulting from a process deviation. However, if Valve X were built using a GROCK template, if it opened during validation, the control module for valve X would log this, and when the log was compared to the FRS, **it would be identified that the phase executed an action that was not specified in the FRS**. Traditionally, this type of error will only be discovered by performing a line by line peer review of the code per the FRS. This type of review in general can only be accomplished by an experienced programmer at very high cost. The premise for Validation Logging is, 'if something is logged and IS NOT specified in the FRS or 'if something is not logged and IS specified in the FRS,' it is incorrectly programmed and needs to be fixed, period. No exceptions!

Validation Logging is not needed after the system is validated. Therefore, we designed in a unit level variable that enables or disables Validation Logging. When testing is being performed, Validation Logging is turned on and when normal manufacturing operations are being performed, Validation Logging is disabled.

Using Validation Logging, Genzyme has experienced a substantial reduction in the time required to create test protocols and execute software changes. Prior to using the methods described in this article, 80% of an automation project was spent in documentation and testing and only 20% in engineering work. Some have argued that 20% engineering is too high. Now, writing test protocols is a simple matter of reproducing the FRS documentation with instructions to check off the steps documented in the FRS are verified with the Validation Logging report. Validation Logging saves time when testing software not only during the original project, but throughout the life cycle of the software. Anytime software modifications are done that require re-testing, the Validation Logging is enabled to re-execute the test protocols using the protocol SOP. It is truly *"the gift that keeps on giving."*

Business Results

The first project we did under this approach was a small microfiltration skid having 28 unique phases and about 100 I/O. Although this project was small, it consisted of a number of different types of control modules which required a significant investment in developing our library. When this project was completed, we had developed 40% of all the control modules that are typically found in a biotech plant. The next project included three identical chromatography skids. The project consisted of three procedures, 11 operations, 29 phases, and one graphic, only one additional control module needed to be engineered. All other control modules were reused from the microfiltration skid project. We realized more than a 50%—cost reduction, and a schedule cut of eight weeks. The software was completed prior to the skid factory acceptance test.

The next project was a 1200 I/O expansion in our Allston Facility called Suite 2. At the completion of this project, the GROCK contained greater than 93% of all the control modules typically found in our biotech facilities.

The rProtein project in Belgium is the first major installation where we are applying the techniques on a large scale. Before cost and schedule benefits for the project are presented, it is worth noting some of the contractual details. Typically, on a project of this scale, >5000 I/O points, the end user would negotiate a Fixed Price contract; essentially paying a higher price than required, but receiving the benefit of the systems integrator absorbing much of the risk for the project; the risk of the unknown. For Genzyme, this idea of paying a higher price for risk mitigation is not required. Having implemented the strategy in three projects to date, we have a strong basis for assessing the project cost. We know, in general, how many hours it takes to build a phase, operation, procedure, graphic, new GROCK module, I/O database, design specification, testing…Where is the risk? So what is now best for Genzyme is managing the project on a time and materials basis. The software development proposal for the Belgium project was more than 30% less than similar scope projects based on industry data. Currently, we have completed the control system software development four months before mechanical completion of the Belgium facility. In addition, we have delivered the control system software more than 10% under budget and plan to have the software validated prior to mechanical completion of the facility.

Validation Benefits

There also are many cost and schedule benefits from a validation standpoint. By using an SOP to validate all phases, operations, and procedures, costs associated with protocol generation are reduced by greater than 95%. OQ Protocol approval cycles are cut by nearly 75% and discrepancies associated with protocol errors are virtually eliminated.

Quality Barrier

Since we now have an established, robust, and validated module library and a finely tuned structure for FRS, DDS, batch software, and protocol development, we can now see the schedule benefits from the design. We refer to this as "In the Bank;" work that is complete and reused, in its entirety, from project to project.

Effort that is "In the Bank" doesn't have to be completed on the next project. Therefore, we can deliver all of the elements of a project much faster. Most importantly, though is the ability to ensure that all documentation matches up before we move on to the next stage of the project. Those documents are:

- Functional Requirements Specifications
- Piping and Instrumentation Diagrams (P&IDs)
- Input/Output (I/O) List

When these documents don't match, i.e., there is a valve on the P&ID that is not in the I/O list or FRS etc., this adds considerable risk to the project - *Figure 4*. Genzyme has instituted a Quality Barrier; a step to ensure that all documents line up before the detailed design and implementation phases begin -*Figure 5*.

Total Project Optimized Solution

With the concept of a quality barrier and "In the Bank" engineering, we have found that implementing automated processes at Genzyme now can be done much faster than previous. Software can be completed and validated prior to mechanical completion of the facility and new products can be brought to market earlier than traditional products - *Figure 6*. The benefits gained by bringing a product to market earlier can substantially outweigh even the 30% savings in software development.

Conclusion

Applied by us or anyone else, the concepts of developing and maintaining standards, leveraging object oriented software to reduce the quantity of testing, and automation validation documentation should perhaps be viewed most importantly as a solution to a business problem—that of the extraordinarily high costs in time and money of implementing automation in a validated environment. The focus can not be just on ways and means. These are only the tools. We have found that it is easy to be blinded by tools, especially technology. Someone has to constantly step back, look at the business problem, and redirect efforts as necessary.

The new concept is not just about technology, however. Vital is the need to make sure each company department and every person involved understands the concept and buys into it, and that everyone reads from the same page in the automation of the plant. Building and applying pre-validated control modules requires that precise and tightly disciplined procedures be followed. Manufacturing, engineering, validation, quality assurance, and management must be in lock step on this. Continuous education and constant vigilance are required.

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This article discusses the gases that are used in production processes in the pharmaceutical industry.

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Regulations Governing Gas Used in Pharmaceutical Production

by Catharina Nilsson, Katrin Åkerlindh, and Anders Ernblad

Introduction

The supply of gases for pharmaceutical production is one of many areas subjected to authority regulations that are passed down along a distribution chain. Regulations originating from the FDA, for example, are directly aimed at pharmaceutical producers, producers that also are audited by the same authority. These demands are then transmitted along the distribution chain back to the suppliers themselves. A supplier, in turn, may then need to order specific materials from its sub-contractors so that the pharmaceutical producer will be able to meet these demands.

Gas is used in many applications within the pharmaceutical industry. Pharmaceutical laboratories, for instance, often have need of high-purity gases. Gases also can be used as secondary coolants in closed systems, i.e., systems in which a product is not exposed to the gas. However, this article focuses on gases that are used in production processes in the pharmaceutical industry. In such cases, the gas in question may come into contact with the product. The purpose of this article is to review common gas usage in the industry and to discuss the different regulations affecting process gas. This article also will illustrate the differences between medical and industrial gases, as well as discuss what the pharmaceutical industry ought to expect or demand from process-gas manufacturers.

How are Gases Used in the Pharmaceutical Industry?

Gas - which is used in a number of applications throughout the pharmaceutical production process - can be considered a component, a utility, a raw material, or a processing aid. The gas that is mainly used in pharmaceutical production is nitrogen - *Table A.* Other gases that are used, albeit to a smaller extent, include oxygen, carbon dioxide, argon, and air.

Nitrogen and argon, for example, are often used for conditioning and transport of pharmaceutical products as well as for storage. These gases are used both during the manufacture of Active Pharmaceutical Ingredients (APIs) and in the production of final pharmaceutical products.

Gases such as oxygen, ammonia, and carbon dioxide act, of course, as reagents in a process, and are thus commonly used during the synthesis of APIs. Hydrogen can be used for hydration, in reduction processes, or to harden fats, and compressed air is often used for fermentation.

Table A. Use of nitrogen in pharmaceutical production.

Blanketing, storing highly volatile substances
Purging process elements of oxygen, moisture or other unwanted materials between processes or at start up and shut down
Sparging or bubbling nitrogen through a liquid to remove oxygen
Transportation/propulsion of materials from one site to another
Neutralizing hydrogen
Mixing liquids without mechanical devices
In liquid form, for cryogenic storage
Removal of VOC by cryogenic condensation
Displacement medium for sterile equipment
Non-oxidizing displacement medium in pharmaceutical vials
Anti-oxidizing of vegetable oils during the heating of the propellant used in pressurized aerosol type dispensers

Nitrogen

Nitrogen, which is inert, is used in numerous pharmaceutical production applications. It is particularly resorted to when there is a need to avoid degradation by oxygen. Well-known applications within the pharmaceutical industry consequently

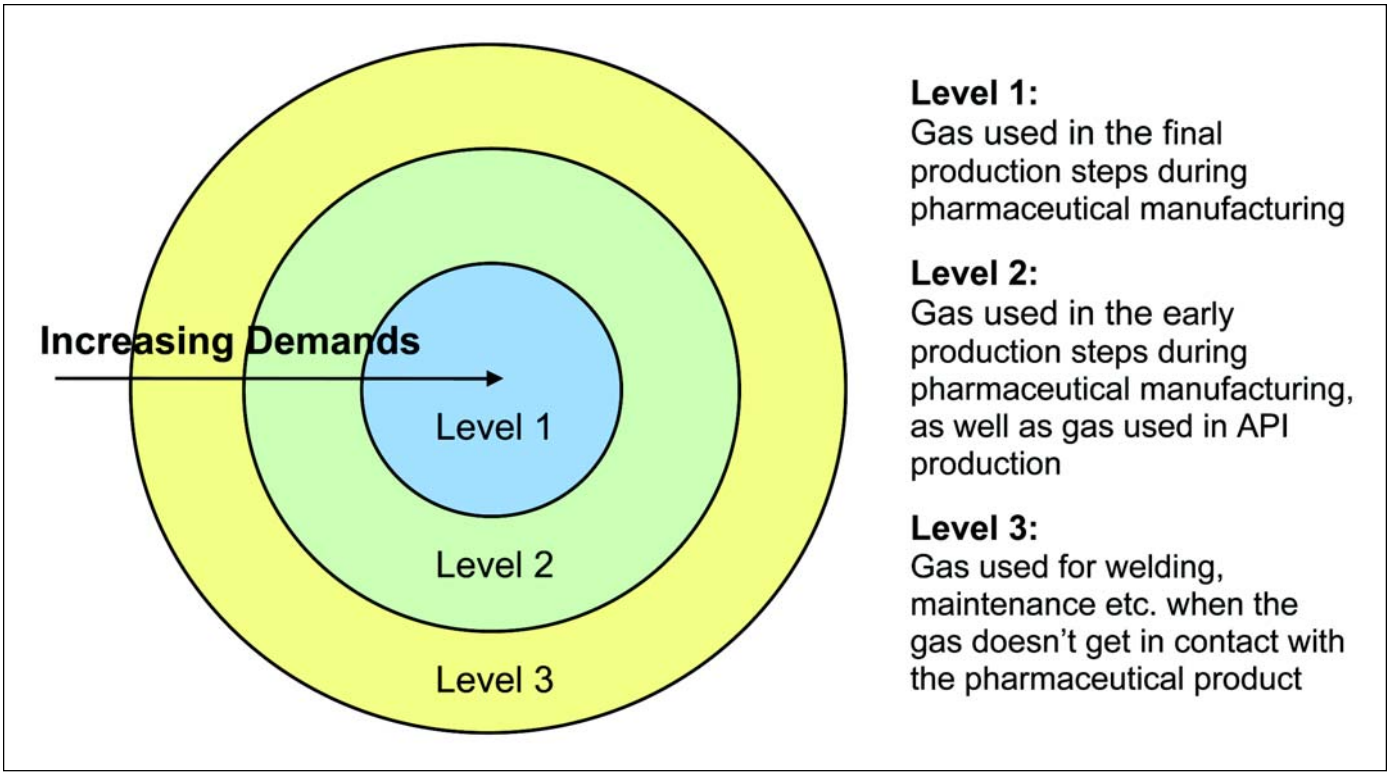

Figure 1. Quality demands on process gases with different usage.

include inerting, blanketing, and purging.

Inerting is performed by using nitrogen to reduce the oxygen level below the minimum level that will support combustion. This eliminates the risk of an explosion, and consequently allows the system to be situated anywhere from the standpoint of safety, as long as safe venting of the inert gas is ensured.[1]

Safety is always of paramount importance when storing highly volatile substances and solvents. Blanketing with nitrogen is a method for constantly maintaining a protective layer of gas on top of the API or pharmaceutical solution. Humid air in the headspace is replaced by nitrogen. A precise-valve control system ensures that as the tank is filled or emptied, the nitrogen content is automatically supplemented to maintain the protective blanket.

The atmosphere within process reactors can be purged of oxygen and moisture at startup or shutdown using nitrogen. Since no pumps are needed, the danger of sparks and subsequent ignition is eliminated.

Liquid nitrogen also can be used for controlling the temperature of chemical reactors, as well as for vapor-emission control based on cryo-condensation. Applications for cryogenic grinding with liquid nitrogen make it possible for a user to avoid overheating the products during conditioning in a mill.

Oxygen

Oxygen is commonly used to enrich air and to enhance oxidation. In biological processes, it also can be used to increase the rate of the process itself, such as in fermentation, or in the cultivation of mammalian cells.

Carbon Dioxide

As of today, carbon dioxide is primarily used for packaging and cooling. Interest in using carbon dioxide for extraction and other super-critical processes, nevertheless, is on the increase. It also is used with incubators, as well as in the production of biopharmaceuticals. As with oxygen, it can be used for the cultivation of mammalian cells. Furthermore, solid carbon dioxide, i.e., dry ice, can be used for cleaning surfaces similar to sandblasting.

Gases Used for Production of Pharmaceuticals vs. Medical Gases

Not more than five percent of the total gas used in production in the pharmaceutical industry consists of oxygen and carbon dioxide or other gases. In other words, nitrogen is the most commonly used gas in pharmaceutical production. It is often supplied in accordance with specific requirements found in pharmacopoeia monographs. Therefore, it may be confused with medical gas, but there are important differences between a medical gas and an industrial gas used in pharmaceutical production. The most notable difference is that medical gases are prescription drugs that must be dispensed by hospitals and pharmacies only.[2]

In the European Union (EU), medical gases are divided into two classes: medicinal gases and medical-device gases.[3] Medicinal gases are classified as medicinal products, i.e., drugs, or active ingredients. These gases often have a metabolic transition within a patient. Medical-device gases are not intended to be physiologically active. They are, for example, often used invasively during surgery or for blood-gas analyses.

In short, medical gases are intended for pharmaceutical use only. Therefore, the production of these gases needs to be in accordance with Good Manufacturing Practices (GMPs) and other applicable regulations. Medical gases are specifically reviewed in EU-GMP, Annex 6, and in the FDA's draft guidance "CGMP for Medical Gases" of May 2003.

Industrial gases used in the production of pharmaceuticals are not required to be produced according to GMP since they are not medical products. Instead, it is the purchaser of the gas, i.e., the pharmaceutical producer that is required to comply with the applicable regulations. The GMP requirements directed toward the pharmaceutical producer include the control of raw materials and incoming components. This means assuming responsibility for obtaining a traceable gas of suitable quality.

Regulations and Harmonization

In judging gas quality, the applicable pharmacopoeia monographs are often used as reference, being well known both by pharmaceutical producers and regulatory bodies.

The various authorities in the US, the EU, Japan, and other countries have different regulations. Work is now being carried out to harmonize these requirements in order to simplify the situation for pharmaceutical producers. The International Conference on Harmonisation (ICH) aims to harmonize technical requirements, whereas the Pharmacopoeial Discussion Group (PDG) works toward convergence and harmonization among US (USP), European (Ph.Eur), and Japanese pharmacopoeias.

The two major pharmacopoeias—with which most pharmaceutical producers want their process gas to comply—are the US and the European pharmacopoeias. However, the demand for compliance with the Japanese pharmacopoeia is increasing as companies export pharmaceuticals to Japan.

With regard to the gases themselves, the different pharmacopoeias differ not only in their specifications as seen in Table B, but also in their recommendations of different analytical methods. The US Pharmacopoeia relies heavily on detector tubes for the analysis of impurities, whereas the European Pharmacopoeia recommends analytical methods that incorporate more sophisticated technology. The Japanese pharmacopoeia primarily recommends wet chemistry methods and therefore has few numerical threshold values for impurity specifications.

The PDG is not currently working with the harmonization of monographs on gases, and it is unlikely that they will be considered for harmonization in the near future.

Regarding nitrogen itself, the European pharmacopoeia has two monographs: 'Nitrogen' for medicinal use, and 'nitrogen, low-oxygen.' The latter monograph was introduced as late as June 2003, and it is especially applicable for nitrogen used in inerting finished medical products that are particularly sensitive to degradation by oxygen.[4] The low-oxygen monograph requires significantly less analyses than the nitrogen monograph for medicinal use.

The US pharmacopoeia is in the process of revising all medical gases monographs. The first set of revisions was published in Pharmacopoeial Forum in the fall of 2002.[5] Briefly, the proposed changes for the monographs include:

- changing assay analysis of oxygen to use a paramagnetic oxygen analyzer instead of the current testing methods
- replacing assay analysis of nitrogen and medical air with an analysis of the oxygen content made with a paramagnetic oxygen analyzer
- changing the assay tests for carbon dioxide, helium, and nitrous oxide to chromatographic methods that have a higher level of accuracy, precision, and reliability than the current official test
- adding a test for air in carbon dioxide

	Ph.Eur Nitrogen	*Ph.Eur Nitrogen, low-oxygen*	*NF Nitrogen*
Nitrogen	min 99.5%	min 99.5%	min 99%
Water	max 67 ppm	-	-
Oxygen	max 50 ppm	max 5 ppm	max 1%
Carbon dioxide	max 300 ppm	-	-
Carbon monoxide	max 5 ppm	-	max 10 ppm
Argon	-	max 0.5%	-
Odor	-	-	none

	Ph.Eur Oxygen	*USP Oxygen*
Oxygen	min 99.5 %	min 99 %
Carbon dioxide	max 300 ppm	max 300 ppm[1]
Carbon monoxide	max 5 ppm	max 10 ppm[1]
Water	max 67 ppm	-
Odor	-	none

1. Oxygen that is produced by the air-liquefaction process is exempt from the requirements of the tests for Carbon dioxide and Carbon Monoxide

	Ph.Eur Carbon Dioxide	*USP Carbon Dioxide*
Carbon dioxide	min 99.5 %	min 99 %
Carbon monoxide	max 5 ppm	max 10 ppm
Nitrogen monoxide and Nitrogen dioxide	max 2 ppm	-
Nitrogen monoxide	-	max 2.5 ppm
Nitrogen dioxide	-	max 2.5 ppm
Total sulphur	max 1 ppm	-
Hydrogen sulfide	max 1 ppm (test)	max 1 ppm
Sulfur dioxide	max 2 ppm (test)	max 5 ppm
Water	max 67 ppm	150 mg/m^3
Ammonia	-	max 25 ppm

Table B. Specification requirements of pharmacopoeia monographs for nitrogen, oxygen, and carbon dioxide.

Except for the assay analysis of oxygen, the proposed changes do not approach USP to Ph.Eur, but instead merely update the technology recommended in USP. The Compressed Gas Association (CGA) has provided comments to the USP monograph change proposals, and the revision of the monographs is still in process.

Regulations Governing Gas Used in Pharmaceutical Production

As discussed, gases used in pharmaceutical production need not be produced in accordance with GMP. Instead, they should be considered components, raw material, processing aids, or utilities from a pharmaceutical manufacturer's point of view.

To a large extent, nitrogen is used for inerting - which has been considered non-critical - and hence, historically, no specific requirements have been made on the gas. Nitrogen of industrial quality has therefore been used.

However, pharmaceutical products entering an inert atmosphere created with nitrogen inevitably become exposed to the gas. This has been noticed by the authorities, and focus regarding the view of process gas has shifted since the late 90s. The FDA considers gas of industrial quality to be a potential source of adulterants. This has resulted in a transfer of responsibilities as regards the demands placed on process gas, which no longer only affect pharmaceutical producers, but also gas manufacturers.

Figure 1 illustrates the quality requirements on process gas used in the production of pharmaceuticals. Level 1 in the figure represents gas that comes into contact with pharmaceutical products in the final production step. Level 2 represents gas that comes into contact with the product in earlier production steps, and Level 3 represents gas used for maintenance, welding, etc. Demands on quality thus increase as the pharmaceutical product moves through the production chain.

In looking at USP/NF, USP is found to contain legally recognized standards of identity, strength, quality, purity, packaging, and labeling for drug substances, dosage forms, and other therapeutic products. The National Formulary (NF) contains standards for such products as excipients. Nitrogen is found in NF,[6] and oxygen has its own USP monograph.[7] While frequently encountered in pharmaceutical production, oxygen is not considered an excipient, but rather a type of oxidizing agent because of its reactivity.[8]

Requirements on Purchased Material

When process gas is considered a component in pharmaceutical production, the FDA requires that the pharmaceutical producer prepare written purity, strength, and quality specifications for the gas.[9] The FDA also requires that the pharmaceutical producer test each component for all written specifications.[9] Alternatively, a certificate of analysis from the component supplier may be used if the pharmaceutical producer validates the supplier's analytical test results at appropriate intervals.

Thus, in order to fulfill GMP requirements, pharmaceutical manufacturers need to have either:

- a rigorous control system that checks all incoming components for all appropriate written specifications, or
- a supplier control system that allows relying on analysis reports received from the suppliers

As in the case of producers of final pharmaceutical products, API manufacturers are required to buy raw material and processing aids that adhere to an agreed specification from approved suppliers. The approval of a supplier should include an evaluation that provides adequate evidence that material meeting the specifications can be provided in a consistent manner. Before reducing in-house testing at the API production plant, full analyses should be conducted on at least three received batches. Even when in-house analysis is reduced, full analysis should be performed in parallel at appropriate intervals and compared with the supplier's certificate of analysis.[10]

In the FDA's GMP guide for finished pharmaceuticals,[9] it is stated that the pharmaceutical manufacturer may buy components against an agreed specification, provided that at least one specific identity test is conducted on the delivered component by the manufacturer.

For API producers, the requirements are less stringent than for producers of final products. API production can be seen as Level 2 in Figure 1. For API producers, "at least one test to verify the identity of each batch of material should be conducted with the exception of the materials described in [Q7A] 7.32. A supplier's certificate of analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers."[10] The materials described in 7.32 include processing aids, hazardous or highly toxic raw material, or other special material, and specifies that for these materials, the API manufacturers need not perform in-house testing if a certificate of analysis is obtained from the supplier showing that the material conforms to established specifications.[10] Processing aids are defined as "materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction."[11]

Among API manufacturers in the Scandinavian countries, a trend can be distinguished to define process gases such as nitrogen as processing aids, in order to be able to rely on a certificate of analysis from the supplier, and not need to perform the identification test otherwise required.

Control of Suppliers

The additional testing that a pharmaceutical manufacturer needs to perform on the received gas is a way of controlling the gas supplier. The pharmaceutical company also should audit the gas supplier's production sites as a way of ensuring that the information on the received certificates is correct. Typically, nitrogen, oxygen, and argon are produced by air separation, and audits ought therefore to be performed at the air-separation plant.

Pharmaceutical manufacturers should assure not only that the gas fulfills the requirements regarding the specification, but also that the analytical methods used comply with pharmacopoeia requirements, or have been validated in accordance with official guidelines. The analytical instruments should be qualified. Calibration of the analytical instruments should be made at appropriate intervals and documented.

Another aspect is the suppliers' quality system, which should include documented production procedures, and also procedures on how changes are managed. Especially interesting is how the changes are being communicated to the pharmaceutical producer. As for the gas supply, one important aspect of change is pharmacopoeia monograph updates.

The fact that pharmaceutical producers perform audits at the gas supplier's production site shows how demands from authorities have been pushed along the distribution chain. When the FDA audits the pharmaceutical manufacturer, they are checking that the suppliers have been approved.

FDA's Quality Initiative

In the FDA's new risk-based approach to pharmaceutical cGMP for the 21st century, steps have been taken to move from the traditional audits of pharmaceutical manufacturers, toward system-based inspections.[12] System-based inspections have a risk management approach and focus on operating systems. The system-based inspections are an initiative from the FDA in order to use resources in a more efficient way, and to have more focused inspections. The inspections build on knowledge gained from previous inspections as well as scientific and technological developments.[13]

Six systems are defined: quality, facilities and equipment, materials, production, packaging and labeling, and laboratory controls. Inspections can either be full or abbreviated. A full inspection includes coverage of at least four systems, one of which is the quality system. An abbreviated inspection includes coverage of at least two systems, and, similarly to the full inspection, one of the covered systems should be the quality system.[14]

The materials system includes materials and activities to control finished products as well as components—including water and gases—that are incorporated into the product, containers, and closures. Areas to be covered during an inspection of the materials system include the following gas-related areas:[14]

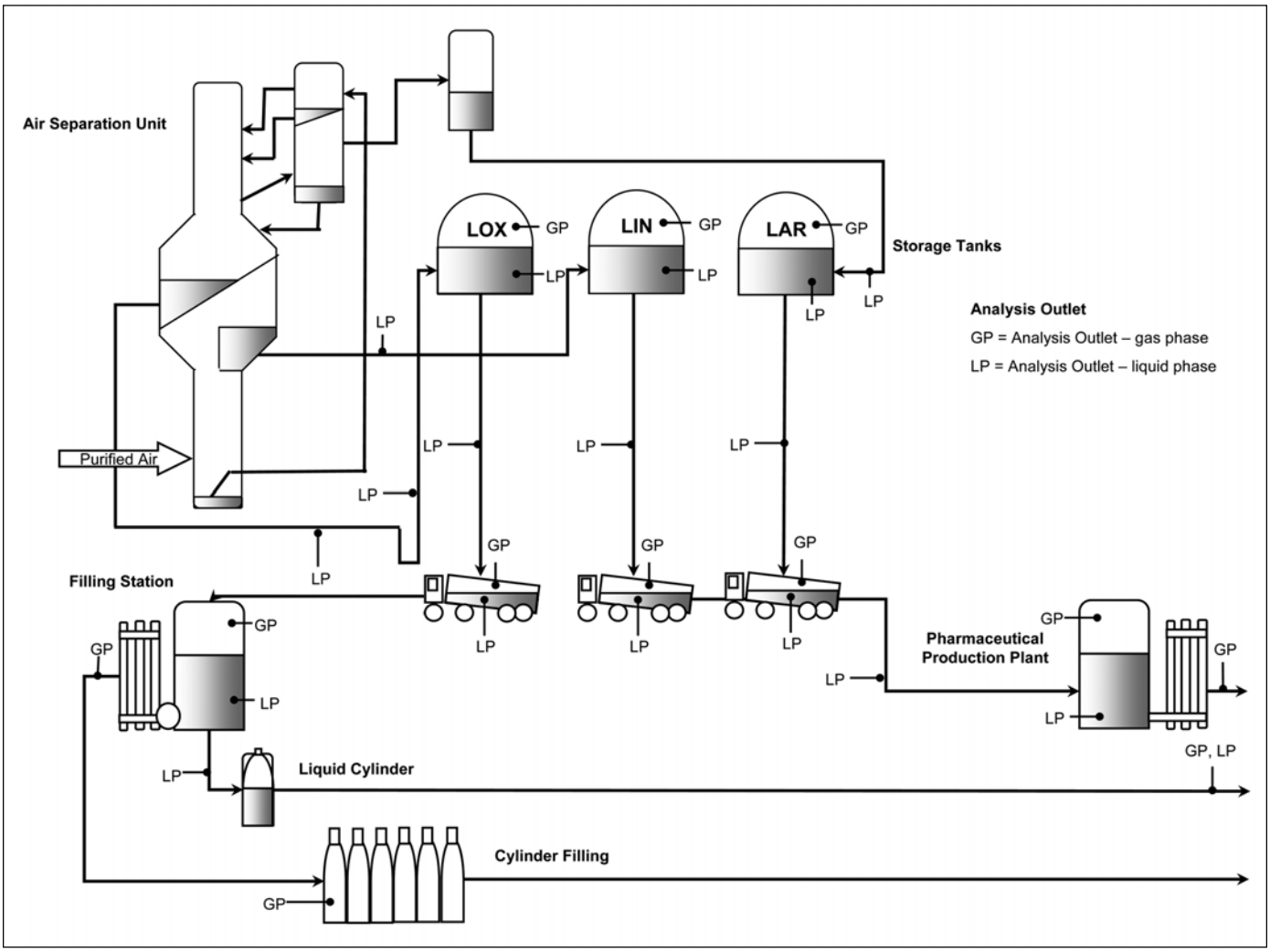

Figure 2. Where to analyze in the distribution chain. LOX = liquid oxygen, LIN = liquid nitrogen, LAR = liquid argon.

- identification and inventory of components, containers, closures
- at least one specific identity test conducted on each lot of each component
- testing or validation of supplier's test results for components, containers, and closures
- water and process gas supply, design, maintenance, validation, and operation

In particular, the last area suggests that the FDA is now concerned about process gases and recognizes them to be used both in non-critical processes and in critical processes, where the API or pharmaceutical is exposed to the gas.

What Can the Pharmaceutical Producer Expect from the Gas Supplier?

Air gases, i.e., nitrogen, oxygen, and argon, are primarily produced through air separation, whereby the air components are separated from each other by means of their different boiling temperatures. The proportions of gases in air are approximately 78% nitrogen, 21% oxygen, and 1% argon. Repeated distillations divide the air into pure gases.

Analyses

The production of air gases is a continuous process, and hence analyses for impurities are made continuously during the gas production. After production, analyses are made at several points before reaching the customer - *Figure 2*.

For gases filled in cylinders, the batch definition is natural. However, for liquid gases supplied in bulk, batches need to be defined because the production process is continuous. For medical gases, the definition of a batch should be documented and related to the analysis of the bulk gas.[15] This batch definition also can be used for a process gas. Consequently, a batch can be defined as the amount of gas in the storage tank before loading, or the loaded tank truck, as long as the batch represents the amount of gas on which specific analyses are made.

There is, of course, a big difference between believing and knowing that gas quality meets specifications. One can only know for certain when a reliable gas analysis has been made. Apart from a suitable instrument, there is the need for gas sampling lines, valves, and calibration and zero gases, as well as for an operator who can manage the whole analytical system and judge when results are reliable, and when they are not.

By using qualified analytical instruments and turning to analytical methods recommended in the pharmacopoeias, or validate analytical methods that give equal or better results, a gas manufacturer will be able to supply gas that has been analyzed in accordance with the requirements from the pharmaceutical industry.

Documentation

To receive gas in accordance with an acceptable specification is self-evident, regardless of the end user. For the pharmaceutical industry, the minimum specification requirements are found in the pharmacopoeias. In addition to the received gas, documentation is needed to prove that the gas complies with the agreement between the pharmaceutical producer and the gas supplier. As seen earlier, the authorities exercise a large amount of control over the incoming material and require all material to be traceable.

By choosing a gas supplier that is able to deliver gases according to the pharmacopoeia monographs, the pharmaceutical manufacturer is able to transfer some of its responsibilities to said supplier.

The bulk supplied liquid gas is added to the storage tanks containing the same gas from previous deliveries. In the case of bulk liquid gases for medical use, results of a sample must show that the quality of the delivered gas is acceptable.[15] This can be applied to deliveries of liquid process gases as well. In order for the pharmaceutical manufacturer to be able to pass an audit from, say, the FDA, the incoming bulk gas should be bought against a specification that fulfills the production demands - and at least the requirements of an applicable pharmacopoeia monograph. The gas should be supplied along with a certificate that specifies the quality and guarantees traceability back to the production.

Installations

The authorities also require that pharmaceutical producers should have qualified systems for utilities such as steam, gas, compressed air, heating, and ventilation.[16] As with gases, documentation is vital. Over and above the gas deliveries that range from ultra-high-purity gases for laboratories to bulk gas in accordance with pharmacopoeia monographs used in production, most gas companies also are able to offer engineering expertise regarding gas systems.

The qualifications performed on the gas system are Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). During OQ and PQ, gas samples are taken and analyzed against an agreed specification.

For the gas systems, there exist specific demands on the pipe material used, components chosen, welding, cleaning, and so forth. A general guidance on the requirements is found in the ISPE Baseline® Guide on Sterile Manufacturing Facilities.[17] One example is the manufacture of sterile products for which design considerations regarding the nitrogen system include:[17]

- nitrogen quality must meet product specification
- materials of construction should be compatible with any external sanitizing agents or internal sterilants (steam)
- 5 µm or better pre-filtration, although 0.2 µm filtration at point-of-use if it is a sterile or aseptic application

- the distribution system design should include sampling points

Conclusion

Gases can be considered many things when used in API, pharmaceutical, or biopharmaceutical production. Depending on what is being defined, the rules and regulations concerning the deliveries may vary slightly. What is certain is that process gas handling is no longer overlooked or ignored by the authorities during audits at pharmaceutical production plants. The FDA specifically mentions process gas supply, design, maintenance, validation, and operation in their risk-based inspection guidelines.

The various authorities require that pharmaceutical manufacturers have a supplier control system in place. This includes control of incoming products and audits of the supplier's production sites. The supplier is required to have documented production procedures, and proper analytical methods and equipment, as well as a quality system including procedures for announcing changes to the customers. This way, not only the pharmaceutical producers, but also the authorities, help in pushing the demands down the supply chain. The more the pharmaceutical producers demand from the gas supplier, i.e., in terms of analytical instruments used, delivery options, etc., the more they can be certain of having 'ready-to-use' process gases delivered to their production plant.

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