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New ISPE President and CEO Sets the Tone for ISPE's Work Ahead

Nancy S. Berg took the helm of ISPE in January as the new President and CEO. In the few weeks since her arrival, she has been working to focus ISPE around its core competencies and key areas for strategic development. This article introduces Berg's view on the role of ISPE and the important link between Members, leaders, and staff.

Integrity and Accountability on the World Stage

ISPE was founded in 1980 by a handful of people who believed the pharmaceutical industry needed an organization that would deal with practical applications of science and technology for technical professionals. Their aim was to improve efficiency and best practices in pharmaceutical engineering to ultimately ensure the quality and safety of medicines.

Thirty two years and 20,000 Members later, Nancy S. Berg believes it's time for ISPE to shine its light brighter on the world stage. As an independent organization with a Membership of leaders, influencers, and decision-makers representing all areas of pharmaceutical manufacturing, Berg says ISPE's work can help support a more positive perception of pharmaceutical companies and their employees. Now more than ever ISPE can serve as a beacon for an industry at the crux of myriad challenges and higher expectations, said Berg.

"Many professionals believe that our industry gets a bad rap, and I think they're right," said Berg. "This happens, in large part, because of the importance of the work we do. Our industry makes products that are life-changing and life-sustaining and they impact hundreds of millions of people worldwide. When the cost of a drug increases or there are problems with a new medication, the public feels the consequences. In these cases, it's a natural reaction to assign blame. Often, it may appear to some members of the public that pharmaceutical manufacturing professionals don't take their responsibility to manufacture drugs safely and cost-effectively as seriously as I know they do."

One of my main goals is for ISPE to do a more effective job of communicating the high levels of integrity and accountability met by pharmaceutical companies and their employees," said Berg. "One of my goals is for ISPE to communicate more effectively around how pharmaceutical professionals and companies work to protect the quality and safety of medicine. The fact that

more than 20,000 industry professionals are members of ISPE, an organization dedicated to sharing best practices and knowledge to protect the world's drug supply, is a testament to how seriously the industry takes its responsibilities. ISPE's Members are the industry thought leaders around the systems that support effective manufacturing, including Quality by Design, superior process characterization, and rigorous compliance management. Our Members run contemporary manufacturing operations, maintain detailed regulatory understanding, and highly progressive manufacturing operations across the global supply chain."

Integrity and Accountability Behind the Scenes

ISPE leaders and staff are working behind the scenes on new strategies that continue to elevate ISPE, and that create better quality

"My vision is for ISPE to focus strategically on the issues of concern to Members, Members' companies, and regulatory leaders, and to be an asset in strengthening manufacturing education worldwide."

education, publications, and networking activities.

According to Berg, three qualities of the most successful associations are 1) a reputation for good value with a portfolio of high quality programs, publications, services, and communications, 2) a contemporary, inclusive, and enjoyable culture, and 3) a rapid response infrastructure that is able to collaborate effectively in order to quickly seize opportunities and communicate information to its Members and industry.

ISPE's success will be defined and measured by the growth and influence of its Membership and programs and being known for contributing value to industry. "My vision is for ISPE to focus strategically on the issues of concern to Members, Members' companies, and regulatory leaders, and to be an asset in strengthening manufacturing education worldwide," said Berg.

In 2012, ISPE will focus on the areas of Knowledge Management and Professional Development, Strategic Marketing, Membership Development, and Regulatory Affairs, and around achieving Enterprise Excellence. Plans for 2012 and beyond will focus on more effective processes for capturing, developing, and presenting ISPE's knowledge through a comprehensive technical strategy, building on relationships with Regulatory agencies around the world, and leveraging all the assets and strengths of ISPE in communication, marketing, and relationship development.

As an organization, ISPE will be globally focused in its delivery of industry knowledge and technical content and dedicated in serving as an independent facilitator of issues of interest to companies, regulators, and Members. "Our brand will be strong and representative of the men and women whose lives are dedicated to keeping the world's drug supply safe and effective," said Berg.

Meet Nancy Berg

Nancy S. Berg comes to ISPE with a career that has made her uniquely prepared to help ISPE as it moves forward with a new strategic plan and a new vision of the Society's role in the global pharmaceutical industry.

Berg has more than 30 years in technical association leadership, along with experience as an entrepreneur and business consultant to commercial and non-profit organizations. From 2000 to 2006 she served as executive director/CEO of the Society of Manufacturing Engineers (SME), where she directed the day-to-day operations of the $30-million/year, 200-employee organization and its worldwide businesses. Areas under her direction included events and expositions, magazine publishing, technical communities, membership operations, and the SME Education Foundation.

At SME, Berg repositioned and streamlined operations, established a more customer-driven culture and integrated product and market development initiatives. She designed and launched the association's strategic plan, Plan 2010. Berg and her management team were recognized by leading professional organizations, such as the American Society for Training and Development and the International Association of Business Communicators, for these efforts.

Prior to being selected as SME's executive director and general manager, Berg was director of expositions, responsible for overseeing 21 domestic trade shows and pavilion events at foreign trade shows. Under her leadership, SME's tradeshow activities grew exponentially and SME was named a top 10 trade show management company in the 1997 and 1998 Tradeshow Week Data Books. As a result of Berg's strategic leadership, SME grew to have four of the nation's top 200 trade shows recognized by Tradeshow Week. During this time, Berg spearheaded joint ventures, partnerships and strategic alliances with more than 100 associations, agencies, governments, institutions and organizations around the world.

Throughout her career, Berg has been recognized as a ground-breaking leader. During her tenure with SME, she was the youngest person to head a global engineering/technical organization. She has been named one of Detroit's "Top 100 Most Influential Women" by Crain's Detroit Business and one of Michigan's Top 50 Women by Corp! Magazine. She also received the Women of Achievement Award, Business & Industry by the YWCA of Western Wayne County Michigan.

Berg has been engaged in education and business issues at local, state and national levels. She has been recruited to serve on many government initiatives involving business, community, development, growth, revitalization and labor issues. She served on the Board of National Science Foundation-sponsored educational coalitions, as well as other boards and committees. She is a fundraiser for the Leukemia and Lymphoma Society's Team in Training Program cycling events and the March of Dimes. She is a leader in her church and has served as professional advisor to executives and companies across many industries.

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Biopharmaceutical Manufacturing in the Twenty-First Century – the Next Generation Manufacturing Facility

by Mark F. Witcher, PhD and Jeff Odum, CPIP

This article presents how the next generation of biopharmaceutical facilities can be designed and operated using recent enabling technologies to improve flexibility, decrease COG, and increase throughput of a manufacturing facility.

Background

Increases in product demand, concerns about product quality, reducing environmental impact, Cost-of-Good (COG) pressures, and recent technical developments in the biopharmaceutical industry have added significantly to the challenges of designing, building, and operating manufacturing facilities in the 21st century.

Continuing expansion of the Contract Manufacturing Organization (CMO) business to facilitate the industry's access to various platform technologies and manufacturing resources, along with an increasing need to rapidly achieve development as well as preclinical, clinical, and commercial manufacturing objectives, present significant additional manufacturing facility challenges. The multi-product CMO business model is applicable to current non-CMO companies as well as future, high performance internal product development and manufacturing organizations. Manufacturing short multi-product campaigns for clinical and commercial products adds to the complexity of running biopharmaceutical manufacturing. Additional challenges are provided by the running of performance qualification batches (conformance lots), inventory building for product launch, and variability in product demand, both above and below market forecasts. The development and launching of biosimilar products also will also present many additional manufacturing challenges.

With this as the backdrop for the "current state," manufacturing facilities must rapidly achieve first-time high product quality, minimize environmental impact and energy consumption, be flexible in initiating and completing manufacturing campaigns, and achieve high throughput to reach competitive COGs targets. With increasing in-vivo insights into product Critical Quality Attributes (CQA) requirements and improving in-vitro analytical protein characterization methods, the critical path for the development and manufacturing of new products will inevitably shift from clinical timelines and more toward the operational timelines of process development and manufacturing organizations.

Case Example

An example of future manufacturing challenges is the U.S. Department of Health and Human Services' Biomedical Advance Research and Development Authority (BARDA) pandemic flu vaccine manufacturing business model as stated in their recent request for proposal "Centers for Innovation in Advanced Development and Manufacturing."[1] The business model requires the very rapid, large scale production of several new pandemic flu vaccines based on pandemic sample viruses (reference virus) obtained from new threats identified in the patient population.

Simultaneous vaccine development, screening, and manufacturing combined with FDA's evaluation for safety, purity, and potency of these vaccines will present a wide variety of challenges. The BARDA proposal requires that clinical material for testing from the first commercial lot be available within 16 weeks of receipt of reference viruses, and 50 million doses be available for release within four weeks from initiation of clinical testing. The vaccine or vaccines would be rapidly released under FDA's EUA Guidance[2] rather than the usual Biological License Application (BLA) release mechanism. The production rate for such a capacity equates

to producing at a rate of roughly 600 million doses/year. To control costs and improve the likelihood of success, the business model calls for the pandemic vaccines to be developed and manufactured within an operating CMO facility. The challenges of supporting pandemic flu vaccine manufacturing when added to the challenges of running a multi-product CMO business will require exceptional flexibility, reliability, and operating discipline capable of doing development, clinical and commercial manufacturing simultaneously.

Organizational mechanisms and facility resources must be provided for developing and operating large scale processes very rapidly with minimal interference to on-going internal or CMO client's processes. Although the pandemic vaccine effort will take precedence, responsibility to support ongoing manufacturing obligations must continue for the cost effective supply of high quality products to the patient population.

These daunting challenges must be accomplished in the midst of a race against the clock to save lives from a potentially rapidly expanding pandemic threatening millions of people. Balancing the various development and manufacturing obligations and responsibilities of the CMO business model and the pandemic flu vaccine requirements will require truly 21st century approaches to biomanufacturing facilities.

Introduction

This article will provide an understanding of how the next generation of biopharmaceutical facilities will be designed and operated to meet these challenges. A number of recent technical advances have created valuable enabling technologies which can be exploited using Quality-by-Design (QbD) concepts to provide improved flexibility, decrease COG, and increase throughput of a manufacturing facility.

The concepts and approaches presented here are applicable to many biopharmaceutical manufacturing facilities regardless of whether the facility is involved in multi-product production of pandemic vaccines or preclinical, clinical, or commercial biopharmaceuticals approved under a BLA.

Biopharmaceutical Manufacturing Elements

For the purpose of discussion and understanding, manufacturing facilities can be divided into three major components: Process (P), Facilities (F), and Infrastructure (I). Each of these three components plays a significant role in the success of any manufacturing enterprise. A failure or weakness in any component will result in poor product quality and/or inefficient manufacturing.

In building a high performance manufacturing enterprise, each component must be carefully created and integrated so that they function as a whole. In the future, the challenge will be to effectively integrate the elements without making them interdependent.

Figure 1 shows schematically how the elements in older generation manufacturing facilities, which were integrated and interdependent by design, can be separated in the future using the enabling technologies into the next generation of facilities. In the past, such interdependency was one of the major reasons that led to the "process defines the product" approach to licensing biopharmaceuticals. In some cases, products produced from different plants using basically the same process were licensed as different products.

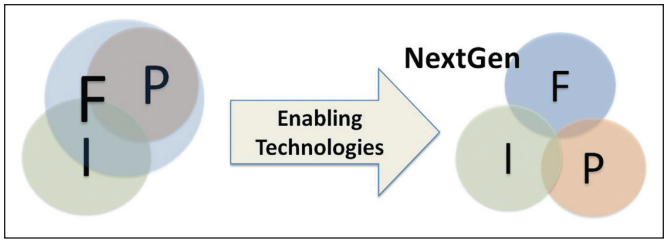

Figure 1. Highly integrated, interdependent elements can be separated using a variety of enabling technologies into integrated elements providing significant flexibility in design, building, and operating the next generation of biopharmaceutical manufacturing facilities.

Using the enabling technologies described below, the elements can be separated into distinct units which can be quickly and efficiently integrated to create a highly effective manufacturing enterprise. To gain further insights, each element will be discussed separately.

Process Element

The process element includes the process unit operations and the equipment required to run the Unit Operations (UO). In the past, the process was defined during development and then implemented during scale-up into specially designed stainless steel systems. More recently, smaller processes have used Single Use (SU) disposable systems which eliminated the cleaning and sanitization requirements.

With the use of skid mounted SU systems, it is possible to have portable process equipment. If the skid mounted SU systems are closed or functionally closed, the process is essentially separated from the facility because the UO skids can be moved anywhere within the facility or even moved to a different facility without impacting the performance of the process.

The process also can be readily cloned to increase capacity by multiplication within an existing facility or duplicated and moved to a new facility quickly and efficiently. The Manufacturing Procedures (MP) and resulting Batch Records (BR) also would be considered part of the process because they are specific to the process as implemented in the SU skids. The process is thus almost completely separated from the location in which it is run.

Facility Element

The facility element is the manufacturing environment required to support the process and process equipment, and includes the building, operating rooms/suites, support functions, such as buffer and media preparation, utilities, HVAC, etc. In the past, the facility elements were hard piped to the process equipment and a thus completely interdependent and operated as part of the process. With SU technology, the supply of raw materials, and possibly even waste materials, can be handled independently from the process thus providing additional functional separation of the process from the facility.

Figure 2. Cleanroom modules that can be configured in different types of larger spaces.

If, as described above, the process is separated from the facility, a wide variety of cheaper, simpler, and more flexible options becomes available for designing and constructing the manufacturing facility. One option is modular cleanrooms that can be assembled faster and cheaper using standard components. Figure 2 shows modular cleanrooms that can be easily configured and assembled into a wide variety of layouts to meet the needs of the processes to be operated.

Infrastructure Element

The infrastructure element is comprised of the people, procedures, and polices used to run the process within the facility. The manufacturing infrastructure is often underappreciated, particularly with respect to its impact on process performance and reliability. In small biopharmaceutical companies, the infrastructure was often specifically designed around the needs of the manufacturing facility. In larger companies, the infrastructure is more standardized across several facilities and is to varying degrees already separated from the facility.

The next generation of facilities must soften these interconnections to meet 21st century manufacturing challenges. The elements can be decoupled using a variety of enabling automation technologies that will be discussed.

Enabling Technologies

Recent developments in a variety of fields have provided opportunities to meet the challenges presented by 21st century requirements. These technologies are discussed in four major categories: Process, Single Use, Regulatory, and Automation. Each of these technologies have significantly improved and expanded over the previous decade. With continued development and implementation, they will provide better tools for meeting future manufacturing challenges.

Process

The first enabling technology is the significant improvement in yields and throughput of recently developed state-of-the-art manufacturing processes. Improvements in cell culture processes have resulted in at least a 10x improvement in product yields with another 2 to 5x improvement on the horizon from specially designed production cells resulting from advances in molecular biology.[3,4] Although, upstream cell culture processes have been most impacted, developments in downstream processing should be made in the next few years to reduce volumes and improve throughput in harvesting and purification processes.

Improvements in downstream processes should come in two areas. First, improvements in cell lines should reduce contaminating and impurity protein loads that require downstream capacity to remove. Second, specialty cell lines should be able to selectively manufacture target proteins while minimizing the overhead of removing difficult to separate product variants. The net result will be significant reductions in overall volumes that need to be processed in order to manufacture sufficient quantities of therapeutic proteins.

The net result of these process improvements is a profound decrease in the number of liters required for upstream processes which results in smaller bioreactors and fewer lots to manufacture the active protein; and significant volume reductions in the purification unit operations required to purify the protein to meet therapeutic requirements.

Single Use Technology

The second enabling technology is the Single Use (SU) or disposable component technologies. SU technology was originally developed to reduce the need for cleaning and sanitization, and the need to validate these steps for single or multi-product operations.

While the economic advantages of SU are complex, they have documented advantages to fixed stainless steel systems in a number of areas. However, the advantages of SU technology goes far beyond simple economics. Because SU systems are closed, or functionally closed, they can be safely and effectively operated in less stringent environmental classifications, such as Controlled, Not Classified (CNC) spaces.

However, as there are "functionally closed systems," there is likely to be, from time-to-time, dysfunctional closed systems which create a wide variety of actual, but perhaps more importantly, perceived opportunities for cross contamination between unit operations. SU technology provides a powerful tool for simplification and standardization of all product contact operations. This advantage can be exploited in a number of ways. When combined with portable skid based operations, the processes can be replicated and/or moved to the significant overall advantage of the manufacturing enterprise.

Regulatory

A third, but less intuitive, yet critically important enabling technology is the increasing sophistication of the regulatory and operational framework in which products are developed and manufactured.

FDA's 2011 Process Validation Guidelines[5] in particular provide powerful tools, when used in an iterative QbD approach to provide excellent operational characteristics for the manufacturing processes. The design, qualify, verify paradigm provides a mechanism for developing a process which operates reliably and assures high quality product. The guidance provides an approach to achieve the necessary operating excellence required to achieve high first-time product quality. The ICH-Q8 defined design space[6] concept requires the use

of good engineering and manufacturing practices very early in the product development cycle. This requirement can be exploited to safely integrate a wide variety of manufacturing functions within the modern manufacturing facility.

The ICH-Q8 defined Real-Time Release Testing (RTRT) approach requires that the process be properly designed with verification tools using Process Analytical Technology (PAT) concepts to assure that the appropriate Critical Quality Attributes (CQAs) and Critical Process Attributes (CPAs) and Critical Process Parameters (CPPS) and Critical Control Parameters (CCPs) are monitored and control to defined standards to assure product quality. The performance of the process is monitored and compared to CQA values to support continuous improvement strategies in support of RTRT.

Automation

The last enabling technology is the use of computers to automate various business and process activities and tasks. Manufacturing processes can be automated using on-line sensors to monitor CPPs and CQAs. The use of process sensors and control methods is typically called PAT within the pharmaceutical industry; and Advanced Process Control (APC) in chemical and petrochemical industries which have significantly more experience with sensor and process control methods.

Using PAT in SU based processes requires the development and use of cost effective disposable, single-use sensors. Development of these sensors is currently an area of significant research and development and many new sensors are becoming available. Direct Digital Control (DDC) systems provide APC and PAT capability to monitor and control processes in real-time. As SU sensor technologies evolve, the ability to monitory processes in the SU world will improve. These technologies provide powerful tools for managing information and controlling the process to assure, and in most cases, guarantee adherence to procedures and ultimately provide high product quality.

Automation of business practices provides significant opportunities to control manufacturing operations. These tools include Materials Resource Planning (MRP-II) systems which facilitate material control and tracking functions. Laboratory Information Management Systems (LIMS) facilitates the tracking and storage of testing samples and information associated with off-line, in-process, and release testing. When integrated with Electronic Batch Records (EBR), all laboratory information can be tracked and used within manufacturing along with real-time information from the DDC system into the EBR to assure tight control of manufacturing operations.

Another tool is the positional control of all equipment, personnel, and materials. Using bar codes or other Radio Frequency Identification (RFID) systems, every component used in manufacturing can be logged and checked in the manufacturing records. Manufacturing operations and sequences can be similarly registered and if necessary controlled as part of the manufacturing record. The DDC, EBR, MRP-II, and LIMS are integrated together in a Manufacturing Execution System (MES) to provide excellent control and eventually RTRT capability within the manufacturing organization.

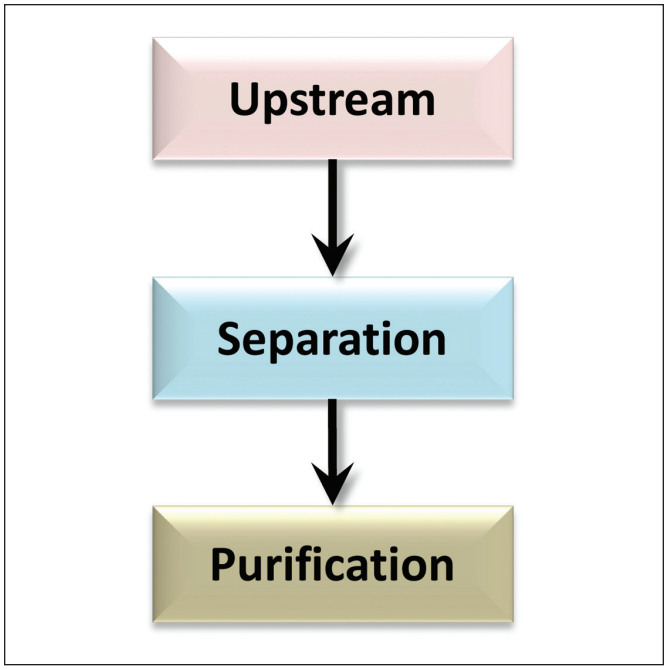

Figure 3. Generation facility with sequential operation of special, purpose built stainless steel process equipment.

Evolution of the Next Generation of Manufacturing Facility Design

Facility designs can be characterized as having passed through three different generations. The initial biopharmaceutical manufacturing facilities were constructed primarily as single product facilities. At the time these facilities were designed, it was an open question as to whether multi-product facilities were either desirable or viable. The possibility of mixing different products and/or processes, such as cell culture and microbial processes was in question.

Figure 3 shows the overall sequence of unit operations. In some cases, purification was subdivided into pre and post viral inactivation and upstream operations were segregated into inoculum and bioreactor suites. The plants were relatively large because early processes were inefficient with low upstream cell titers and inefficient suboptimal downstream processes.

These plants were constructed so that the process was carried out in fixed stainless steel systems. In the case of some facilities, multi-product capability was implemented on a

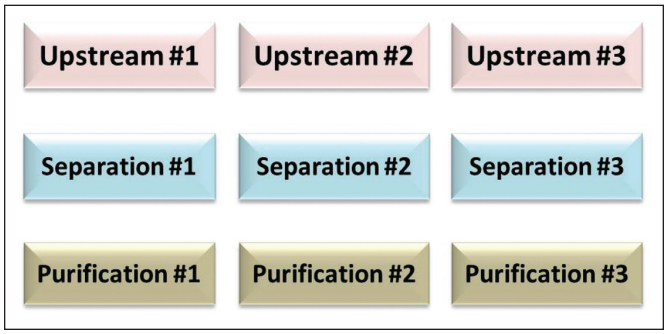

Figure 4. Generation II – CMO based design to accommodate multiproduct operation. Upstream, separation, and purification areas operated independently.

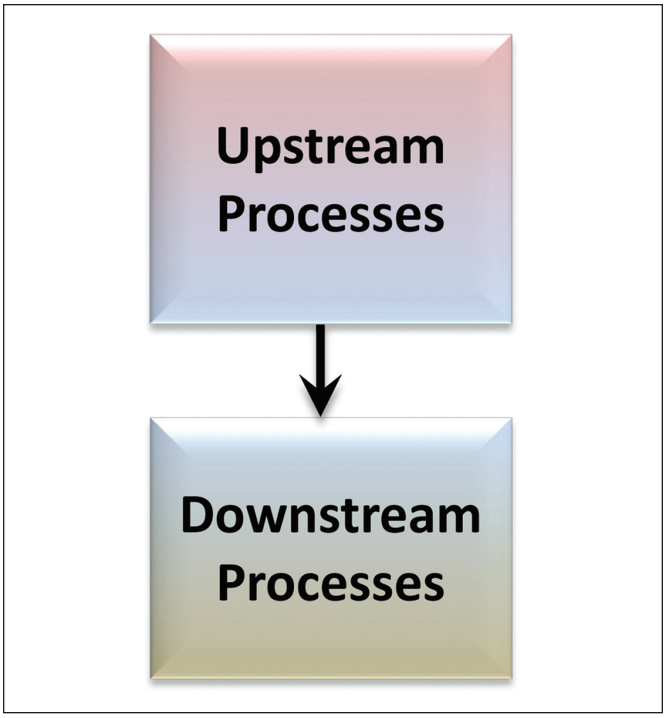

Figure 5. Generation III facilities where processes with secondary containment are operated in larger spaces.

campaign basis by removal of the first product and installation of the second product within the facility. The fixed systems were adapted to the second product as best as possible with alterations and additions to the fixed system as needed.

In an effort to support multi-product CMO like operation, the second generation facilities were designed with multiple suites of each type. In some cases, the suites were of different sizes to permit appropriately sized suites to be used for each manufacturing campaign. Such a facility is summarized in Figure 4 as a second generation facility.

Generally, the facility was designed with hard piped stainless steel systems with fixed media and buffer preparation systems that required CIP systems for cleaning followed by clean steam sanitization. As SU technology became available, some of the smaller volume operations, such as inoculum and small scale final purification steps, were supported by disposable equipment.

As SU volume capabilities increased, the design of the facility began to switch to the next generation which sought to combine UOs into larger rooms. The central concept behind the Generation III facilities is that the SU technology provides closed or functionally closed system that would permit multiple UOs to be run in the same area without the potential for cross contamination. As volume capacities of SU technologies also began to increase, particularly upstream operations, SU could be applied to a larger number of processes and products.

Figure 5 shows the basic concept of combining operations into larger spaces. Because the processes are more contained, the use of CNC spaces could be considered for upstream, separation, and early purification processes.[7,8,9] Final purification steps are typically located within appropriately classified spaces. Figure 6 provides a generic layout of this conceptual approach.

Next Generation Manufacturing Facility

Based on looking at the operational aspects of using the enabling technologies, the following is a discussion of the next generation of manufacturing facilities (NextGen). Using the QbD concept of designing the facility to maximize the operability and throughput of the facility, the approach discussed calls for a facility that segregates the process into small rooms within a "Manufacturing Matrix" shown in Figure 7.

The manufacturing matrix can be divided into three types of spaces. The first are Cleanrooms (C.R. #1 thru 4) where processes, which might have one or more open steps or some other reason for using a rated cleanroom space, would be run. Typically, final stage purification operations would be executed in classified spaces. The second type is Controlled, Not Classified (CNC #1 thru #4), where processes which are closed or functionally closed can be operated.

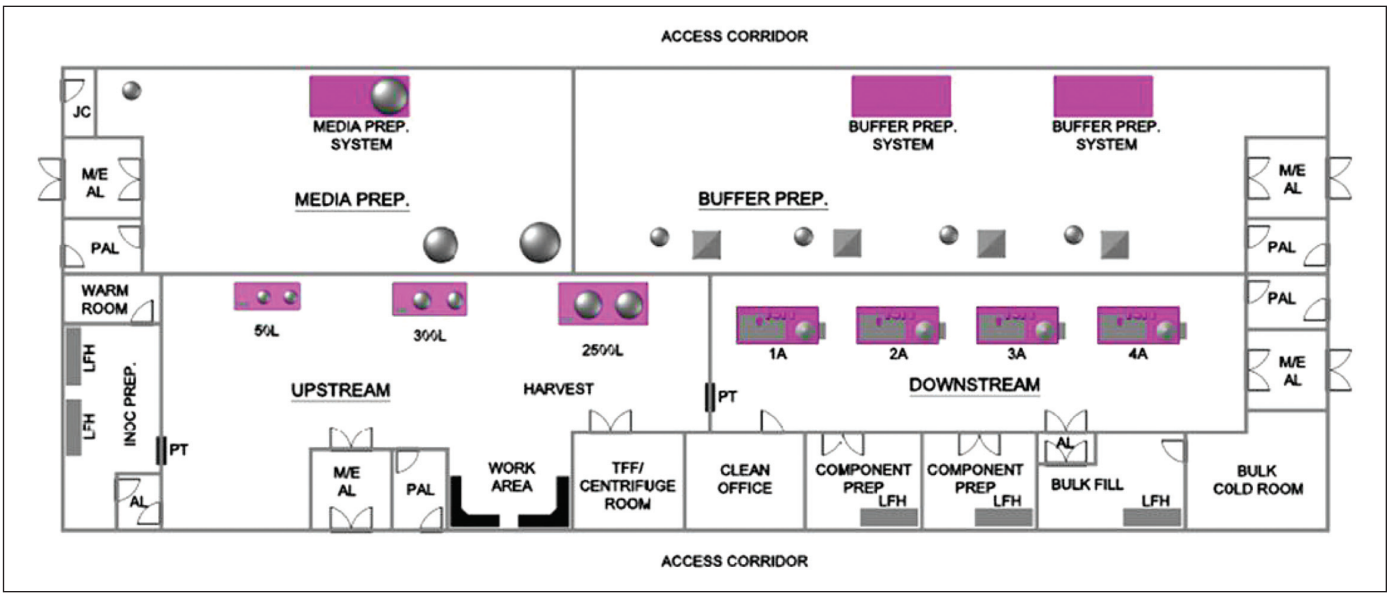

Figure 6. Generic layout of Generation III facility for a cell culture based process.

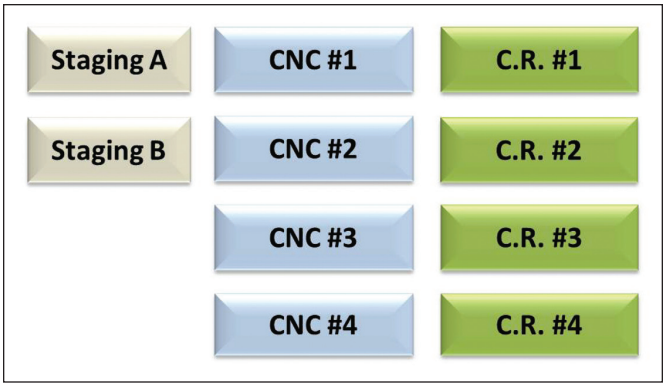

Figure 7. Process areas for preparation and operating of process unit operations. Matrix is a mixture of CNC and cleanrooms. Staging areas are CNC and could be used to run processes if available.

The third type of space is Staging Areas (A and B). Staging spaces are used to assemble the equipment and prepare the systems for operation inside the manufacturing core of CNC or classified spaces. Assembly would include collecting the required non-electronic documents, if any; collecting certain raw materials, setting up skids; and assembling appropriate SU parts such as sensors and tubing sets. Training, shakedown runs, and other setup tasks also can be completed. The value of the staging areas is that it provides a segregated non-high value space to prepare the systems for operation and a place to store the readied systems until the appropriate high value space becomes available. The prepared equipment can then be very rapidly moved into the operating core and quickly run with a higher assurance that the properly prepared process would operate as designed. Staging areas also can be used to prepare systems for long term storage should significant additional time to complete preparations be required.

As described later, staging areas also can be possibly used to run development or engineering runs depending on their availability within the overall schedule and priorities of the facility.

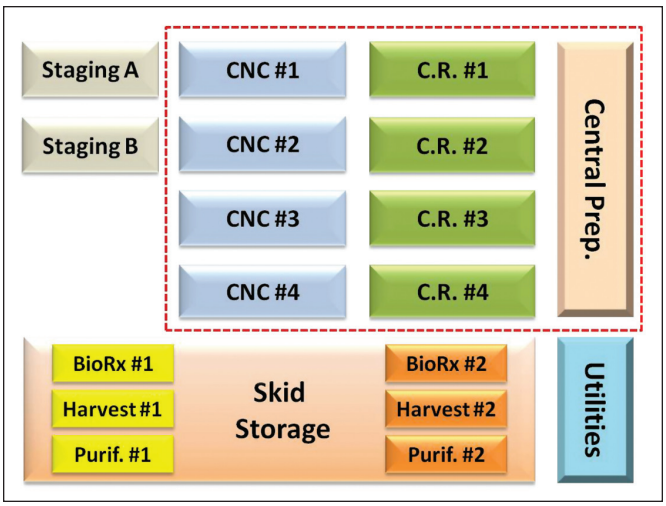

Figure 8. Central elements of the manufacturing matrix with process skids in storage. Central prep. provides raw materials for all process steps. Utilities connected only to central prep.

All the fundamental elements of the NextGen are shown in Figure 8. Raw materials and feed streams for the facility are prepared in central prep. Depending on the processes, central prep could have separate buffer and media preparation areas or multiple areas for each depending on the materials and amounts being prepared. Straightforward support areas, such as offices, laboratories, document storage, waste disposal, etc., are not shown.

Because the facility runs a large number of processes, a sizable storage area is provided to store the process skids and associated equipment. Figure 8 shows two processes in storage which will be shown in operation in Figure 9. Since all equipment within the facility is positionally controlled, the equipment for a particular process can be easily located and controlled at all times.

All elements in the matrix are connected by hallways that provide access to each area. All raw materials are prepared in central prep and distributed to the various operating areas under continuous positional control. Critical utilities are supplied to central prep from an adjacent utilities area. Utilities are not typically supplied directly to operating areas. In some cases, skid mounted utilities, such a process gases, would be supplied to operating areas as needed.

The simplified manufacturing matrix provides several important options for construction. With the rooms being simple CNC or cleanroom spaces, the matrix can be assembled using pre-constructed modules into a variety of configurations. The facility also can be easily expanded, perhaps within an existing inexpensive warehouse to increase the size of the matrix depending on the number for products and processes.

Operating the Manufacturing Matrix

The primary intent of the manufacturing matrix shown in Figure 8 is to provide a manufacturing environment which provides maximum flexibility to operate a wide variety of processes. Because the entire matrix is run using manufacturing procedures (GMPs) and policies designed to maintain the integrity of other products and of the facility as a whole while assuring the production of high quality material, a

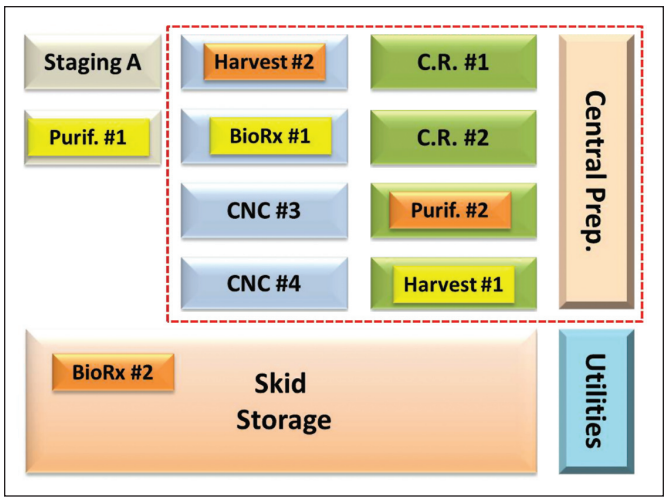

Figure 9. Manufacturing facility with processes in various stages of entry, operation, and storage.

"The biopharmaceutical industry must meet the challenges of rapidly and efficiently manufacturing a wide variety of products, including pandemic vaccines and new therapeutic proteins."

wide variety of manufacturing processes or process steps can be performed in any area appropriate for executing the process. Thus development, engineering, shakedown, preclinical, clinical, or commercial manufacturing operations can be performed within the matrix of operating areas. Depending on scheduling of various manufacturing operations and their priorities, the facility is able to respond to a wide variety of product development or manufacturing demands.

Because the rooms are simple spaces, free of fixed equipment and other hardware, they can be quickly and completely emptied, cleaned, and sanitized in preparation for the next campaign. All manufacturing operations from development to commercial manufacturing would use the same infrastructure tools and be executed using GMP manufacturing procedures developed to assure that each manufacturing operation does not interfere with another manufacturing operation. The key is to make sure that manufacturing procedures executed under well designed GMPs for development runs provide the flexibility to solve developmental problems quickly and efficiently while providing appropriate controls and documentation to assure it does not interfere or interact with on-going or future products. Complete removal of all materials upon completion of the work is assured by the MES documentation and control mechanisms. Such operation will require operating discipline from development, engineering, and manufacturing operators that are required in the 21st century manufacturing environment. The manufacturing matrix in operation is shown in Figure 9.

While two processes (Process #1 – BioRx #1, Harvest #1, and Purif. #1; and Process #2 – BioRx #2, Harvest #2, and Purif. #2) are shown in various phases of manufacturing, the facility could simultaneously support a larger number of processes depending on the length and complexity of each manufacturing campaign. To support more processes, the size of the matrix can be easily expanded.

As shown, Process #1 is being brought into the facility with both the bioreactor (BioRx#1 in CNC #2) and harvest process (Harvest #1 in C.R. #4) in place and operating. The purification process (Purif. #1) is being moved into the facility through Staging B for operation when Harvest #1 is complete. Once the three unit operations for Process #1 have been moved into the facility, they can run the required number of lots to complete the manufacturing campaign.

Process #2 on the other hand is completing its campaign. The purification process (Purif. #2 in C.R. #3) and harvest (Harvest #2 in CNC #1) skids are in place while the bioreactor (BioRx #2), which has completed the campaign, has been removed to the Skid Storage area.

The ability to move processes in and out of the facility quickly and efficiently can greatly increase the throughput of the facility and permit flexibility in responding to changing manufacturing requirements or deal with process problems. Capacity can be significantly increased by cloning the process equipment and installing a second production train. Another advantage of the matrix approach is that processes that require additional segregation, such as pre and post viral inactivation, can be easily separated into different areas within the facility.

Conclusion

The biopharmaceutical industry must meet the challenges of rapidly and efficiently manufacturing a wide variety of products, including pandemic vaccines and new therapeutic proteins. Recently evolving technologies enable the design and building of a new generation of manufacturing facilities which can rapidly support late stage process development, preclinical, clinical, and commercial manufacturing activities for new and existing products. The enabling technologies include advances in upstream and downstream process performance, portable, clone-able single use equipment, improvements in regulatory and operational strategies, and automation of operating and business functions. The resulting new facilities will employ a matrix of simple operating areas which are capable of segregating various unit operations into manageable, high performing units which can be flexibly operated to optimize the efficiency and throughput of the facility. Such segregation methods provide a valuable tool for assuring independent operation and removing any questions associated with possible cross contamination or operational problems associated with interference between different unit operations or products.

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A Holistic Approach to Pharmaceutical Manufacturing: Product Lifecycle Management Support for High Yield Processes to Make Safe and Effective Drugs

by Julie Fraser and Guillaume Kerboul

This article presents a holistic approach to pharmaceutical manufacturing based on product and process knowledge that allows companies to manage data that improves yields, enhances confidence, identifies risk, and manages the complexity of increasingly personalized medicine.

Introduction

The complexity of today's pharmaceutical market requires more efficient drug development and production. Product Lifecycle Management (PLM) has the opportunity to make pharmaceutical production more effective and with lower risk – even in this vastly complex environment. Leaders are actively implementing PLM and are reaping the benefits of fewer problems, lower costs, higher yields, employees armed to make good decisions, and audits that make everyone more confident as they access the information they need.

The Holistic Approach

Holistic, meaning "relating to or concerned with complete systems rather than with the analysis of, treatment of, or dissection into parts"[1] suggests that many elements are involved and interacting. Ideally, processes create continuity in several dimensions:

- throughout the product lifecycle
- across disciplines
- between products and production processes
- among trading partners
- from one generation of product to the next

PLM is a holistic approach to manage products from early concept through all stages of development and production through to end of life. The goal of PLM in any form is to better leverage all available data to improve product and process design, planning, testing, and production. In today's industry, the product lifecycle might end in moving off patent or in splitting into several versions for smaller patient populations - *Figure 1*. Catering to smaller patient populations means an explosion in the number of specific products that need to be tracked, traced, and managed through their entire lifecycle. This is very challenging with processes that are not fully integrated,

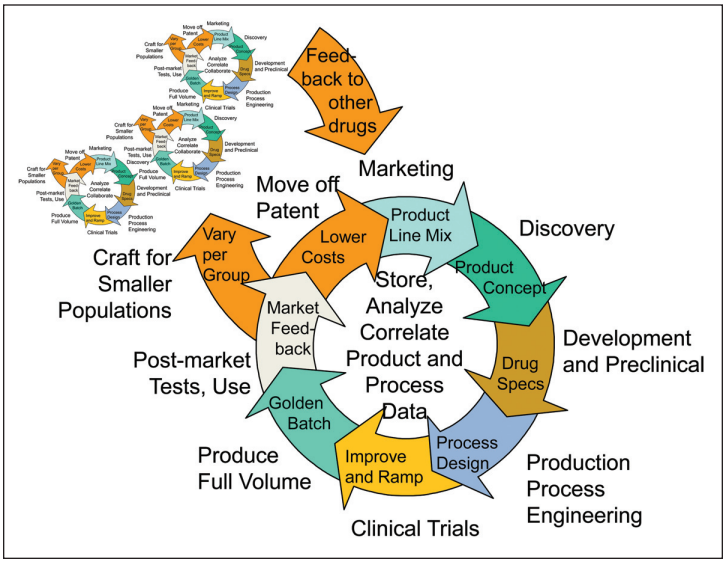

Figure 1. Product lifecycle management is an approach supported by software that can gather, store, and analyze multiple disciplines' data into a useful knowledge repository.

leading to another driver for managing all of these products in a PLM software system.

This ability to build a knowledge base from every aspect of the process contributes to the success of all other aspects and phases of a product's life, and to the success of other products in the portfolio. In the pharmaceutical environment, this reduces the need for regulatory oversight: safe, efficacious products are the natural outcome of this holistic PLM approach.

One initiative supported by PLM is Quality by Design (QbD), outlined in ICH Q8 Product Development standards.[2] While some people think that QbD is purely a statistically-focused approach, the concept is much broader. QbD is a product/process lifecycle approach founded on continuous improvement as the FDA[3] illustrates it in Figure 2. Notice how similar the PLM and QbD models are, each representing a closed loop cycle.

Because of the need for analysis, QbD efforts have used largely esoteric mathematical, analytical, and statistical methods. While these are the critical scientific foundation, they may actually mask the overall holistic QbD program for staff who are not statisticians, but who have an important role to play.

Figure 3a shows the struggle most companies have to achieve QbD or any lifecycle approach. The separate information environments means that the various teams often cannot

Figure 2. Quality by Design is a cycle in which product and process design and performance create a closed loop of knowledge and continuous improvement (source: FDA's view on QbD, Moheb Nasr, 2006).

Figure 3a. Typical current silo state: minimal cross-discipline understanding.

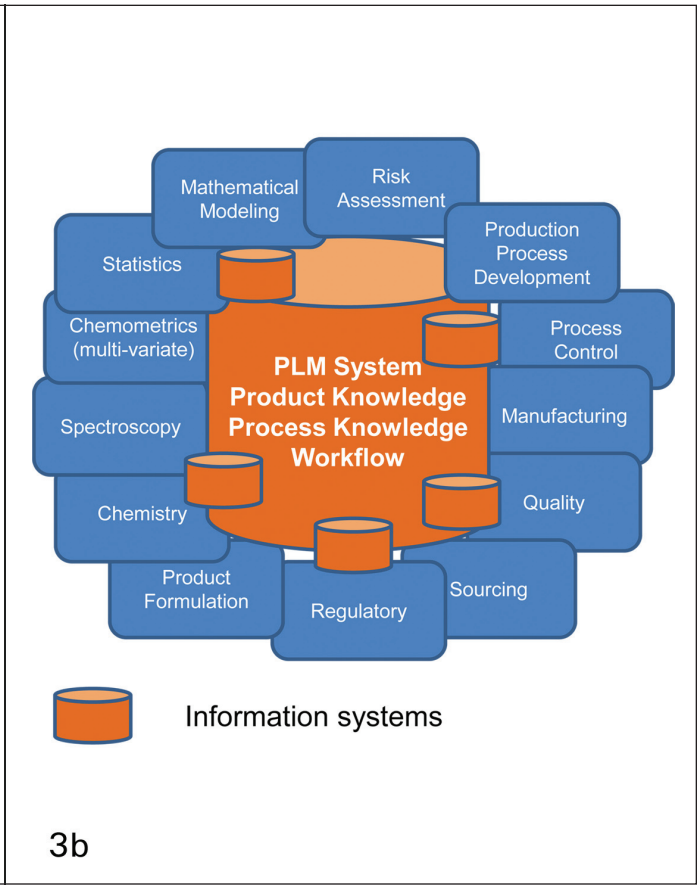

Figure 3b. PLM system support enables cross-discipline knowledge sharing and better context for all groups' decisions.

Traditional multi-disciplinary silos (3a) with independent information systems create challenges that a PLM approach (3b) can overcome with common data management, advanced analysis, and support of knowledge from many disciplines.

leverage each others' work fully. They typically use different terminology, have different viewpoints, use and create different data, and leverage independent information systems. While everyone involved is theoretically striving toward the same goal, these information disconnects can lead to a lack of understanding and incomplete risk analysis.

Figure 3b illustrates the PLM approach supported by a centralized and industry-specific PLM application suite, which for pharmaceutical includes regulatory business process and submission workflows, portfolio and formulation management, manufacturing analytics, supply chain scorecards and sourcing applications, in addition to engineering and equipment design applications. The PLM platform brings together all relevant information and delivers structured processes by which disciplines can work together to proactively improve product quality. Using structured approaches helps to minimize process and product variation and risk. PLM has helped to lower cost, increase yield, and deliver significant benefits to the companies who use it, and to their customers.

For example, in the early product formulation stages, quality, process engineering, and manufacturing are involved to ensure the team fully considers lessons learned from previous products. This helps to prevent blind spots and disconnects, thus reducing risks and timelines. Both QbD and PLM have product yield and quality in mind from the earliest discovery stages. In this way, PLM and QbD also improve innovation, shorten overall product introduction times, and support regulators' confidence.

Obstacles to Quality by Design

Pharmaceutical manufacturing executives must recognize where their current approaches fall short and develop a path to enable company success. Representatives from regulators as well as the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use have presented some of these shortcomings in a systematic way. Briefly, these problematic practices to avoid include:

- **Quality by test.** Off-line analysis can result in low yield, as it allows products that will not pass final tests to go through the process. The result is increased cost, cycle time, and risk, as the company scraps products and requires a second production run to get acceptable quality product out.

- **Issue correction without prevention.** A primary focus in manufacturing on corrective action, not preventative action raises the risk that problems will recur, wasting cost and time. Part of the challenge is that prevention must typically be built into the design of the production process itself, and many companies have processes that are not designed to stay within the boundaries for high quality production outputs.

- **Silos of data and knowledge.** Most companies have data owned by different departments or disciplines. For example, production data from one product often is not readily available for designers of follow-on products and their production processes. The data is in different forms and thus not often used as context for forming an overall knowledge base about the product and production process. This is true from stage to stage (development to clinical trials to full production), but also in some cases among the groups that service production and process development, such as statistics and multivariate analysis, spectroscopy, mathematical modeling, and risk assessment.

- **An empirical or variable-by-variable approach to pharmaceutical development.** This results in a costly and slow process that is also vulnerable to blind spots because it cannot account for the interaction between variables that frequently cause problems in trials and in scaled-up full production. Even in multi-variate approaches, the focus on an average rather than the distribution of outcomes (i.e., minimizing the likelihood of batches that are out of specification) can limit production success.

- **Change-resistant processes.** Once validated, the production process becomes fixed and focused on reproducing outcomes. This limits the companies' interest in pursuing new technologies and process improvements that would result in higher yields at lower cost.

Understanding these shortcomings of the current process development approach, regulators and the ICH have started to promote holistic approaches, shown in the middle column of Table A. Across the industry, leading pharmaceutical producers are beginning to shift their business processes to new approaches that better leverage knowledge.

Pragmatic Ways to Get Started

PLM is a big vision for product and process development, validation, and execution. To gain the benefits, most companies will require new approaches, mindsets, and information flows. The magnitude of the change is one reason pharmaceutical companies have only recently started to move to PLM practices and QbD submissions.

Another is that the software support has been scattered, and is just coming together in PLM software suites recently. The capabilities that PLM software has to support the enhanced approach regulators favor are listed in the right-hand column of Table A. Some pharmaceutical companies have started their QbD journey in specific areas with focused software that fits into a PLM suite and are gaining benefits already.

Eli Lilly is using simulation of code for production process control systems. This software actually runs process design data through scenarios on the company's equipment prior to the first production runs. Eli Lilly's project manager reports their results: "Using this software, our team delivered the project three months early, simulated the whole plant (actuators and sensors), and rapidly implemented the control system while increasing production quality. The integration tests using this tool acted as support for qualification."

Q8 Approaches to Pharmaceutical Development		PM System Support Capabilities
Minimal Approach	***Enhanced, QbD Approach***	
Fixed manufacturing process	Manufacturing process adjustable within the design space	Structured change management based on specifications and analysis
Focus on reproducibility	Focus on control strategy and robustness of the process	Virtual manufacturing with simulation of the process and product outcomes
Off-line analysis	PAT tools used for feed forward and feedback process control	Process design creates control parameters, and data management handles data from process control
Quality assured by testing	Risk-based control strategy (real-time release)	Risk management analysis data stored and in context and accessible
Empirical development	Systematic approach to development	System support for development process using scientific and empirical data
One variable at a time	Multivariate experiment	Multiple variable analysis to minimize out of spec., not average, results
Reactive lifecycle management	Preventive lifecycle management (and continual improvement)	Multi-disciplinary data and collaboration from earliest product/process concept
Adapted from: 10/2008 Presentation: QbD: A Global Implementation Perspective The EU Perspective by Richardo Luigetti of EMEA at the Siena Conference on Product and Process Optimization		

Table A. While ICH Q8 will accept the traditional "minimal" approach, it pushes for the QbD approach, which PLM enables and fosters.

Sanofi Pasteur is using an analytical software tool to understand best practices in its operation. Beyond what traditional multi-variate analysis can do, this software is easier for manufacturing teams to understand and use. "This tool is particularly successful where other, more classic analysis tools fail. By producing simple and explicit rules that explain the functioning of our vaccine production processes and by highlighting the parameter correlations that may cause these processes to deteriorate, this tool helps us to improve process quality, security, and profitability," according to René Labatut, VP Global Manufacturing Technology.

Each company will have its own path to move toward the holistic PLM approach. Specifics will depend on the company's current practices, stages in their products' lifecycles, technologies in place, etc. It's often best to start with a specific product, process, or project to gain confidence, but the goal must be to generate a company-wide shift over time.

In short, moving to PLM will usually need a champion with executive level support to effect the required changes in people, processes, and technology. To keep support, companies must get quick wins. What follows are some basic concepts to help managers get each of these areas started on the journey.

- Participate in training or education or workshops to get your team up to speed. Public sessions relating to both QbD and PLM are relatively common. If only a few of your team or certain disciplines have attended these sessions, we recommend enrolling entire cross-disciplinary teams in overview sessions. As teams begin to share knowledge, they will gain better understanding and begin to establish common terminology and expectations.

- Involve cross-disciplinary teams in designing new processes to move toward a holistic approach. These new processes may focus on creating a knowledge inventory, defining CQAs, reducing variability in ingredients or in processes, formulation scale-up, or simply opening lines of communication between disciplines at critical points in each group's process.

- Technology that is proactive and holistic across the product lifecycle can enable both process change and education. It's important to have the total PLM roadmap in mind, but some companies will start small and build out. There are quite a few possibilities for starting points, including:

  - Leverage a system that supports effective production process design with simulation and verification of results for each product and variant to be produced on that line.

  - Implement a system that helps find quantitative and qualitative data in multiple electronic sources quickly and efficiently to foster early collaboration between product development and manufacturing experts.

  - Use technology to deliver the data and analysis you need to characterize and optimize the manufacturing process. Technologies might include plant data systems to capture actual data from processes and operations intelligence that analyzes product and process data.

  - Set up electronic batch records to enforce processes, make data more coherent and available, and automate according to 21 CFR Part 11. These systems also speed audits, process knowledge gathering, non-conformance analysis, and recalls.

  - Use a tool that can analyze data from manufacturing operations to identify best practices.

PLM in Action

PLM is not just an effective tool for pharmaceutical companies. Global organizations from just about every industry benefit

from it. From these brief case studies, pharmaceutical organizations can learn exactly how to incorporate PLM within their infrastructures to achieve their desired operational benefits.

- A leading helicopter company moved from 467 legacy systems per site/department/discipline to consistent, role-based enterprise systems for 20 core business processes including PLM. PLM was rolled out first because the company wanted to get the core product data correct so they could quickly and fully reposition the business to be more responsive and cost-effective. Pharmaceutical companies can learn from this because they frequently have multiple systems hosting confusing, inconsistent product information. PLM gives one version of the truth for all of this company's employees to access.

- An inspection and metrology tool company went from a customized system for PLM to a new standard platform. They have achieved up to a 10X time to market performance improvement by collaborating with customers, employees, suppliers. Speed to market is a major concern of pharmaceutical companies as they struggle to get products into the market and maximize their time under patent. PLM allows organizations to holistically manage quality and compliance with internal employees as well as outsourced partners.

- An aircraft manufacturer used PLM to reduced problems or nonconformance in their first prototype by 50% by simulating the product and the production process. They are eliminating paper in their production plants. This is an example of how PLM can be used to improve product quality in early stages – equivalent to clinical trial stages for pharmaceutical companies.

Urgency to Improve for Safety and Performance

Companies in every position in the pharmaceutical industry are under unprecedented pressure from regulators and shareholders to improve performance. This typically requires an improvement in manufacturing yield and repeatability. In addition, new opportunities are emerging to serve worldwide markets and in some cases, with drugs targeted to smaller populations offering improved safety and efficacy as well.

With the resulting complexity, pharmaceutical companies must develop a cross-discipline lifecycle knowledge base with instant information access. Other industries with human safety issues and varying global regulations, such as aerospace, defense, and automotive have proven the value of PLM software. While these industries are not finished improving, they have managed to reduce costs, improve efficiency, and adhere to very high quality and safety standards.

The pharmaceutical industry is on the brink of a new era. People, paper, and domain-specific systems can no longer keep up with the complexity and business pressures. Leaders are turning to PLM as a holistic approach based on product and process knowledge. Moving from inconsistent data in disconnected systems to a PLM environment with supporting software allows companies to manage data in a way that improved yields, enhances confidence, more clearly identifies risk, and is capable of managing the complexity of increasingly personalized medicine. All of this is likely to lead to satisfied regulators and happier shareholders.

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This article presents considerations to be made prior to making a capital investment in pre-owned equipment for new or refurbished pharmaceutical facilities.

Application of Pre-Owned Equipment in Pharmaceutical Manufacturing Operations

by Stephen Sirabian, Bob Matje, Jeff Biskup, and Witold Lehmann

Introduction

In an effort to improve access to quality health care, the pharmaceutical manufacturing industry is highly motivated to reduce the cost of its products and to improve efficiency of its operations to provide safe, effective, and affordable medicines. No part of the industry is more pressured to reduce costs while maintaining quality than in the Oral Solid Dose (OSD) products sector. Therefore, it should be no surprise that used manufacturing equipment was a prominent part of the discussion during a recent meeting of the ISPE Oral Solid Dose Community of Practice Steering Committee meeting in Tampa. The general consensus was that a Good Practice Guide on the risks/benefits and how tos of incorporating pre-owned equipment into capital projects would be extremely beneficial for the industry. This article was prepared by members of the committee as a potential pre-cursor to developing a more expansive document. Feedback on this article would be helpful in determining the level of industry interest in the subject and the path forward (http://OSDPre-OwnedEquipmentSurvey.questionpro.com).

The consolidation within the industry has resulted in a growing surplus of high quality equipment that has been reclassified. The challenge is understanding how to find the "good" equipment and how to apply it. This article will provide some guidance into that process and awareness of some potential pitfalls to avoid.

The Business Case

Cost pressures in the industry are increasingly causing us to re-think, re-evaluate, and re-invent ourselves to meet the demands of both rising costs and the need to provide affordable medications to consumers. Further, in the recent wave of mergers, acquisitions, and partnerships (Merck and Schering-Plough, Wyeth and Pfizer, Teva and Proctor and Gamble, Genentech and Roche, etc.) all with the intent of creating shareholder value, have as collateral effects redundant operations, organizations, and assets.

Idle assets in an organization create a waste stream referred to as "waiting" in the operational excellence arena, and waste elimination is a primary goal of a company in order to impact its bottom line profitability. The answer to reducing this waste stream is often the consolidation of organizational capability to allow the efficient use of assets in the network. Industry consolidations often involve the relocation of equipment from one facility to another to either diversify an existing operation or create a new capability at a plant. Either way, a synergy is achieved whether it is re-using idle space, multi-tasking an existing workforce, or optimizing utility capacity.

Further, with a flood of idled, moth-balled, and used equipment on the market, it is very tempting to look at this area as a cost avoidance opportunity to your capital project. After all, who can resist paying cents on the dollar for a new capability? Even if it is not a complete system, or has some manufacturing hours on it, the differential between the cost of buying it new versus used is often believed to be able to make the system fit for purpose and the depreciation of the discounted equipment will have reduced impact on cost of goods, which will mean lower product cost and higher profits margins, right? The temptation is very real.

As with all strategies, planning and risk

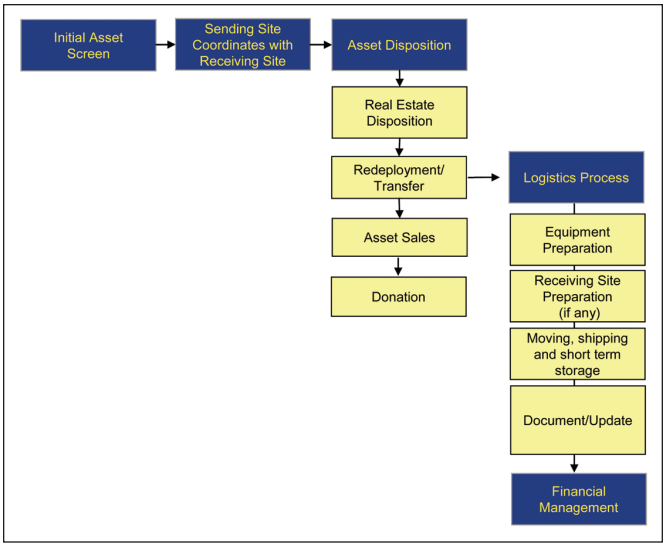

Figure 1. Typical asset disposition process.

management lay at the heart of successful reuse of equipment. At a business level, the economics or business case must be taken into consideration, risks must be weighed, and contingency plans must be evaluated before a final decision is made. Pfizer employs a simple, but effective asset redeployment model that allows teams to quickly assess the most appropriate disposition of an asset - *Figure 1*.

In evaluating the re-use of equipment, one must first and foremost assure that the form of the equipment fits the function or requirements of the process. Many processes are robust enough (i.e., a large design space) that dimensional and operational similarity is sufficient to ensure success, but some processes require dimensional and operational equality (i.e., a small design space). Ideally, a technical assessment should be conducted to assure that the needs of the process are able to be accommodated within the capability of the equipment. The organization's development, scale up, engineering, and technical services teams should be consulted at this point to ensure that the asset being considered for re-deployment is fit for the purpose.

A high level physical assessment should be undertaken to ensure that there is space available at the receiving site and that there are no obvious barriers to allowing the transfer to take place (enough room to install, operate and maintain the system, appropriate utility access, means and methods of transporting the unit to its new location, proper bearing capacity of foundation, etc.)

In addition to the process review and physical assessment, one must consider where the equipment came from, how the equipment was maintained, how complete the system is, what codes and standards it was built to, what documentation is available, and what products were manufactured in the equipment prior to its re-deployment. The more that is known and understood about the system, the better the risk can be managed when transferring it and installing it in its new location. (This is discussed later in the article.)

If your company does not regularly engage in the use of pre-owned equipment or the transfer of products and processes between facilities, there may need to be a close collaboration between the project team and the receiving site to ensure that the receiving site understands what it is receiving, where it came from, the business justification, and contingency plans in the event that the equipment fails to operate as intended. These details should be communicated in the Technical Transfer Plan discussed below.

Lastly, it is important to understand the financial treatment of the asset(s) to be transferred to best determine how the cost of goods (which is ultimately realized in product cost) will be impacted. A high level of collaboration with your finance department is recommended for this effort. If you are transferring the equipment internally, it is important to understand how much of the asset has already been depreciated. Further, it is important to ask how the Net Book Value (NBV) is determined. Does your company's financial policy require that all costs associated with the acquisition of the asset (engineering, installation, commissioning, or validation/verification, etc.) transfer as part of the NBV? This could significantly dilute your cost avoidance objective on a product cost basis and should be considered very closely as part of the business analysis.

After the business conditions have been satisfied, the process(es) have been reviewed, the physical assessment completed, and a risk management plan developed, a product process focused Technical Transfer Plan must be developed to ensure a robust understanding of the execution of the work. A Technical Transfer Plan generally includes the following elements, but can be expanded or condensed as needed to suit the complexity of the transfer:

- Product/Process Description
- Project Charter
  - Statement of Purpose
  - Sending and Receiving Team Identification
  - Risks and Issues List
- Transfer Authorizations
- Technical Gap Analysis
  - Product Formulation
  - Cleaning Process Modifications
  - Technical Risk Assessment
  - Contingency Planning
- Transfer Strategy
  - Sample Request Plan
  - Reference Standards
  - Capital Funding Strategy
  - Cleaning/Packaging/Shipment
  - Stability Plan
  - Artwork
  - Risk Assessment
  - EHS
  - Milestone Schedule
- Regulatory Filing Plan
- Continuous Improvements

Of critical importance to this written plan is a side by side comparison of the current process that is in use for manu-

facturing with the new process. Many times, there will be no change to the production process as it is being transferred from one location to another, but there is often a temptation to upgrade or optimize the process as it is being transferred and while the capital funding is available. Unless the process does not work, is no longer compliant, is not safe, or not economically efficient, it is highly recommended that the process is first transferred, understood at its new location and then optimized. This approach eliminates at least one variable if the transfer develops difficulties.

In the case of purchasing used equipment for a new or existing production process, the same level of rigor should be employed as well as the development of a complete Technical Transfer Plan that highlights any particular scale-up issues.

After the Technical Transfer Plan has been drafted and is approved, pre-transfer meetings should take place to review the details of the removal, transport, delivery, rigging, setting, and handover of the equipment. Further, a detailed review should be undertaken of the documentation that is available and whether this documentation is reusable or needs to be rewritten to accommodate the current intended use of the equipment.

At this time, a validation strategy should be developed. Older equipment that is to be re-commissioned may have been validated using the standard IOQ process, while there may be an advantage to commissioning and qualifying the equipment using the newer ASTM-2500 (CQV) process. This should be determined during the transfer planning stages to ensure that the appropriate documentation and information is collected and roles and responsibilities of team members are assigned and understood, and also to aid the design team in understanding where the validation boundaries are and what valving arrangements, by-passes, instruments, and gauges that may be required to isolate the system and measure the physical characteristics of the process, or allow access for the measurement of the process.

General Planning and Budgeting Issues

Project planning and preparation for a capital project that will be based on the use of used equipment requires special consideration. There are two major drivers for using pre-owned equipment: cost and schedule. On the surface, both look too good to be true and to some extent that can be the case. Even if one expects the unexpected, there still could be significant additional costs and timing-related issues that could drag out the schedule far beyond what one might assume as worst case, yet it still might be a very good deal. A few adjustments to your normal preplanning and budgeting process might help your chance of success.

Scheduling

One of the major benefits of purchasing used equipment is often schedule. Specialized equipment for OSD manufacturing can take many months or close to a year to obtain, so a pre-owned press or fluid bed drier that is ready to move can look pretty attractive and it well may be, but scheduling the decommissioning, relocation, and reinstallation process includes many different factors compared to projects with new equipment. Much of this is due to the fact that the new owner is taking on responsibility for a fair bit of work normally done by the equipment supplier. The other unique aspect of a project using pre-owned equipment is that it was customized for the original owner, not for the new application. Repurposing for a new application can involve a fair bit of effort to evaluate, adapt, and incorporate the pre-owned equipment into an operation for which it may not be perfectly suited. Recognition of the added responsibility is a key to developing a realistic schedule.

Appropriation of Funds

Costs on projects that involve a significant amount of used equipment can be significantly different than normal projects. The equipment costs on the surface will be a fraction of the cost of new equipment. Commonly, early project budgets are often factored from equipment costs, including internal owner costs and external costs for engineering, construction, and other support functions. Historic factoring multipliers are typically based on experience based on the cost of installed new equipment selected to fit the installation. Utilization of used components complicates the budgeting process in two key ways. Cost of the equipment itself is unpredictable and not always easily related to new equipment costs. Additionally, the cost of integrating that equipment into the new facility is likely to be significantly more complex than installations of new equipment components. Since neither of those factors is very consistent, it is generally not very predictable.

When considering the cost of the used equipment, the source of that equipment is an often overlooked issue. Certainly used equipment brokers or other pharmaceutical manufactures may offer the lowest initial price, but some OEM's refurbish

Example				
	New	*Used from Original Equipment Manufacturer*	*Used From Equipment Broker*	*Total Cost with OEM Options to Broker*
Purchase Capsule Machine	$1,000,000	$350,000	$200,000	$200,000
Equipment Considerations				
Warranty	included	included	not included	$20,000
FAT	included	included	not included	$10,000
Change Parts	included	$75,000	not included	$75,000
Installation Costs	$25,000	$25,000	$25,000	
Risk	low	moderate	high	moderate
Schedule	8 months	2 months	2 months	2 months
Facility Considerations	same	same	same	
Validation Standard LQ/OQ	$15,000	$15,000	not included	$15,000
Total	**$1,040,000**	**$465,000**	**$225,000**	**$320,000**

Table A. Equipment cost breakdown new vs. old. (Courtesy: Jacobs Wyper/IMA)

and sell older units, in which case the OEM may provide enhanced support by means of an FAT, partial warranty, or simply a more reliable documentation package. The cost of these various options must be evaluated with an eye on the ultimate cost/benefit as seen in Table A.

Staffing

For the same reasons described above, staffing requirements should be adjusted on projects that include a significant amount of pre-owned equipment. Special expertise will likely be needed to support the evaluation and assessment of the equipment that will be purchased and assure that the repurposed equipment is properly integrated into the new facility. Extra expertise will be needed in several aspects of the project and will be particularly important in the engineering design and commissioning of the facility. The most challenging piece of the whole effort is the ability to recognize which pieces of the puzzle are missing and being resourceful in solving those problems. Parts may be missing from the purchased equipment, or even more likely, interconnecting parts between components/systems will be missing. Resolving that type of problem can take intricate knowledge of the equipment and operation. Allowances should be made so that personnel resources are available when needed to minimize the cost and time spent resolving these problems. Few companies have that kind of resource readily available.

Risk Assessment

The project team should conduct an early risk assessment for the specific project situation. That assessment should include consideration of factors discussed in the preceding paragraphs. The assessment should be revisited throughout the project and updated. Several aspects of the risk assessment are discussed in the paragraphs below.

One significant issue is the risk of cross-contamination caused by API being retained in the motor housing or other near product contact areas that can then cross-contaminate. This is a particular risk for equipment at single dosage stage, such as presses, encapsulators, and coaters. In these cases, sub-microgram quantities can exceed the Allowable Daily Exposure (ADE) and be an issue. The FDA has issued some notable Warning Letters on the need for risk assessment on cross-contamination.

For more details and the risk of equipment that has handled compounds of regulatory concern, *ISPE's Risk-MaPP® Baseline Guide* is a good source of information.

Equipment Considerations and Planning

The myriad issues surrounding equipment decisions in the OSD are vast with process equipment invoking a host of added concerns. While it may be tempting to immediately dive into the details, a structured approach has proven itself most effective in terms of both efficiency and accuracy.

Begin with no assumptions and treat the first phase as a type of triage, in which the equipment's condition is assessed to the point of a go/no-go decision; in other words, can it live on with the proper support or is it time to pull a sheet over it? The goal at this point is to benchmark the situation quickly with a minimum of time and cost, so before taking the time to visit the machine in question, begin with some simple questions.

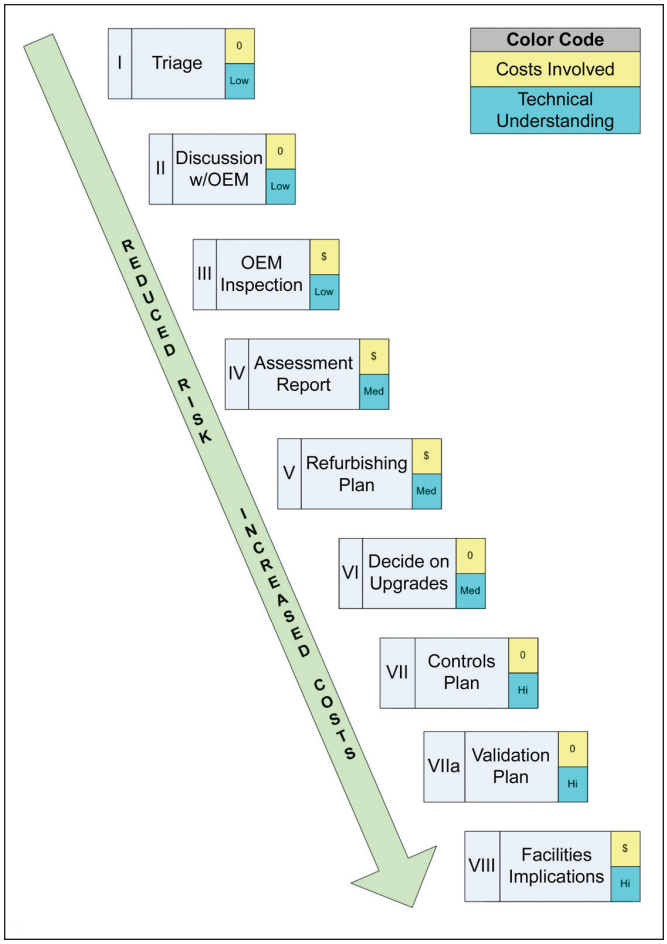

Figure 2. The nine phases of equipment evaluaton.

Start with the nameplate data as well as the identity/location of the original purchaser. The age is an obvious indicator of condition, but if the equipment was moved from its original country one needs to check the quality and thoroughness of conversion to local electric current, standards, and mechanical interface. Changing all the mechanical interfaces and flanges to local standards can be time-consuming, but as long as the electrics have been properly modified, the costs should be reasonable.

A copy of the original specification for the equipment must be obtained at the outset. While there may have been changes throughout the years, this is a simple way to get a quick handle on scope and the original intent since process equipment is routinely customized to some extent. Identifying this and comparing it to your URS/purchasing specification will enable a first-pass gap analysis.

Moving on, we need to get a picture of the life the equipment has led. Has it been fully utilized during its lifetime? How has it been maintained? Find out how many batches have been run, request copies of maintenance records, calibration logs, cleaning SOPs, etc. Typically, decommissioned

pharmaceutical equipment from a pharmaceutical company will undergo a decommissioning process where residuals have been removed, product contact parts have been replaced, and a final calibration has been completed. Having this executed protocol will help determine the state of the equipment. Further, it is important to understand whether the equipment was used for penicillin manufacturing or other regulated substance. Once on site, a visual inspection will create an immediate impression, but bear in mind we are still in the go/no-go phase so this is where a checklist prepared in advance can be extremely helpful as seen in Table B. This is the time to look over the documentation package available, which can be invaluable. If little or no documentation is available, there will be costs associated with developing this documentation, and it cannot necessarily be assumed that the vendor or OEM is able to re-create this information for you. Also, pay particular attention to the diligence spent on post-installation modifications; obviously the vendor's records will not address these.

Assuming there were no obvious quality issues and the machine is close to your URS and capacity, a phone call to the Original Equipment Manufacturer (OEM) is Phase II. Most vendors can call up the background for a given serial number and although confidentiality restrictions will prevent full disclosure, the ballpark price for a new piece of equipment is vital data point. As a rule of thumb, expect to pay 20 to 50 cents on the dollar for used equipment in reasonable condition. If the age of the equipment is known, the OEM can provide a background on major design changes sine that point in time. Most notably, the safety standards of 20 years ago would fall short of a new machine, in which case a conversation with your EH&S team is a necessity. In addition, there may be some innovations that either improve the process conditions or perhaps make the system more efficient in terms of productivity or yield. The OEM can detail these for you simply based on the equipment's vintage and can provide meaningful advice on the true impact these features could have on long term cost. Even saving hundreds of thousands of dollars today may pale in comparison to the lost productivity of a few percentage points of yield over the course of 10 years.

Phase III will involve the first, albeit small, funding expenditure in order to have the OEM inspect and evaluate the equipment in question. If there is any opportunity to do this

Component	Inspection Item	Pass	Fail	N/A	Note
Product Temp Probe	Check probe response.		✓		Replace
	Check for any damage.	✓			
	Check for proper fit.	✓			
	Check condition of gaskets.	✓			
	Check condition of windows.	✓			OK but some scratches
	Check condition of doors.		✓		Bushings and gaskets must be replaced
	Check condition of nozzle ports.	✓			
	Check hinge operates smoothly.	✓			
	Check latch operates freely.	✓			
	Confirm ground strap present.	✓			
	Check operation of limit switch.	✓			
Filter House	Check for any damage.	✓			
	Check condition of gaskets.	✓			
	Check condition of windows.	✓			Minor scratches
	Check condition of doors.	✓			Heavy scratching/repolish
	Inspect vent.	✓			
	Check pressure relief panels and condition of gaskets.		✓		Replace gaskets
	Visually check limit switches.				
Filter	Check for any damage.		✓		Replace filter
	Check for proper fit.		✓		Replace
	Check condition and length of distance ropes.		✓		Cables loose
	Check condition of gaskets/seals.	✓			
	Check inflatable seals for proper pressure.		✓		Replace seals
	Inspect bottom ring/D ring for any damage.	✓			
	Check for ground wire connection.		✓		Replace wire
	Check locking mechanism for proper operation.	✓			
	Check condition of filter cable.	✓			

Table B. Machine inspection checklist – fluid bed.

while the equipment is still operational, all efforts should be made to take advantage of that, even if it means pushing Phase III further up the timeline since this can be invaluable in determining the true worth of the machine. In such cases, allow enough time to run the equipment through all phases of possible operation, including loading, discharging, and cleaning modes. If automated, run several full recipes, even if each recipe step is only a few minutes. The goal is to operate all moving parts through all potential operating modes several times to check for alignment, leaks, even movement, noise, vibration, or any other telltale signs of wear or poor maintenance. Ultimately, this comes down to a matter of risk management since a visual inspection of a static unit is far less meaningful. In these situations, the inspection will focus upon welds, seams, seals, surface finishes, and a sign of improper maintenance, but the potential for uncovering hidden problems is an order of magnitude higher than when the machine is operational.

A formal Assessment Report is Phase IV. This is a written record of the OEMs inspection and will typically run down a check list categorizing various systems and sub-systems depending upon the access and ability to operate the components. It should include an evaluation of which items appear to be in good condition versus those that are questionable and most importantly, the replacement cost and availability for items likely to be replaced. Age of the equipment has a direct bearing on this, as one would expect, but on older units there is a distinct possibility that parts are simply unavailable. This is expected for control systems, where out of date components cannot run with today's software, but mechanical items 10 years old may have been replaced with newer models which are not compatible. In these cases, the assessment report will provide an insight on the practical alternatives and the cost/risk/timing associated with these alternatives.

Spare parts issues must be conclusively addressed in the Assessment Report as they can make or break the project. In the most extreme case, unavailability of a critical part may render an older machine essentially useless except as a source of parts for similar vintage units; more likely, the availability will be limited, meaning the costs and lead times are beyond the norm for more contemporary machines. Obviously the Assessment Report must identify all items no longer available as well as the schedule impact, but it does not stop there. An estimate of how long the parts in question will continue to be available as well as the probability of this are critical as is a recognition that this can only be an estimate as the OEM has limited influence over mundane, but critical components, such as valves, sensors, actuators, etc. Another subtlety is the degree to which replacement items can be seen as "like for like." Again, look to the OEM for advice on this, particularly in pointing out if the differences in the latest generation of a given item has any impact on the ultimate system performance.

Evolving safety standards play a major role in the Assessment Report. As an example, the latest NFPA guideline for baghouse-type dust collectors calls for some form of explosion protection, such as suppression or containment. A 10-year-old baghouse will not be in compliance and the cost and complication to upgrade such a unit may be disproportionate to the difficulties inherent in such work. The electrical classifications are also evolving and must be fully addressed during this phase. Again, if the unit is moving into a different country, these non-compatibility issues should be expected.

Similarly, vessel code ratings can become a major challenge if they were not originally ASME (or equivalent) rated. A manufacturer of new equipment can be held responsible for meeting the original ratings as required by purchase specifications. On the other hand, with used equipment, the original manufacturer is likely no longer involved, thus putting the risk of compliance on the new owner. Used equipment with previous damage or equipment that has been disassembled and moved multiple times may increase the risks for the new owner. These risks are particularly significant in situations with explosion potential. They also would be more significant where replacement or access for potential repair is limited.

During this phase, it can be worthwhile to expand the OEM's role into an evaluation of the de-install/re-install process. Rigging paths should be mapped out with the OEM to determine the extent of disassembly required and its impact regarding reassembly, alignment, and re-commissioning. The OEM should be on site for disassembly to tag wires and tubes, inventory parts, and take note of any conditions requiring attention that are discovered as components are pulled apart allowing closer inspection.

Phase V is a Refurbishing Plan, which goes well beyond the Assessment Report. This plan is a joint effort between the user, OEM, and engineering company performing the re-installation. Too often the Assessment Report is viewed as the end of the evaluation process, when it is actually only the beginning. During this fifth phase, the user must compare the URS with the used equipment's specification and performance parameters, the so-called gap analysis. Here, the functionality of the equipment, assuming it is restored to full operational status, is examined to determine what process compromises will be required. Such compromises can be seen in a variety of areas such as final product quality, batch time, yields, flexibility, operational issues, and cleaning needs. Obviously, the final product quality is the issue least capable of compromise, but rarely can batch trials be run on a used machine, so this requires a leap of faith if the unit is not similar to manufacturing equipment already in operation. Once satisfied that the final product quality can be maintained, the regulatory team must be consulted. Even under SUPAC, there may be a need for revalidation or even stability batches. While not insurmountable, such issues must be quantified in terms of cost and schedule and put into the evaluation equation against the cost of new equipment. Of course, if a case can be made for these issues, the immediate availability of used equipment as compared to new can be a major advantage for a pharmaceutical manufacturer.

Once it has been determined that the machine can do the job at hand, we enter Phase VI and consider upgrade options. Even though the unit may be functional, it may make sense

to commit additional funds to increase its performance level. Using coating pans as an example, humidity control can be added with humidification and dehumidification available to improve the control of the moisture profile in the process. Valves and actuators can be upgraded to so-called smart devices. Fan capacity and pressures can be increased and enhanced. Wash In Place (WIP) can be achieved with the strategic placement of WIP nozzles. On fluid bed processors, simple dryers can be turned into granulators or coaters by adding new inserts or modifying old ones. Tablet presses are often refurbished to get a new lease on life with updated instrumentation and new tooling. Indeed, given the right used platform, the process "guts of the system" can be completely changed out.

Although technically part of Phase VI, controls are treated as a separate Phase VII due to the magnitude by which they can impact a project. Control systems are often upgraded, either to add recipe capability and automation or simply to upgrade outdated operating systems and hardware. Given the pace of modern day software evolution and the consequential impact on hardware requirements, any unit over five years should be viewed with an eye toward upgrade and systems older than 8 to 10 years will likely require replacement. Still, some I/O hardware and communication components may not need to be changed out, so avoid automatically assuming that wholesale change-out is needed.

When dealing with the seller of the used equipment, be sure the latest version of the operating systems and shrink wrapped software is available. The OEM's code has likely been modified on several occasions if only to upgrade service packs from the controls manufacturer. Without this and the source code, troubleshooting will be a guaranteed nightmare as the OEM will be unfamiliar with the changes and the original owner's software team will be inaccessible. Focusing on hardware, check the electrical classification, particularly if you are in anything but a non-hazardous area. The same goes for solvent applications; not only will the motors, sensors, and other field devices require upgrades, but conduit sealing and intrinsic safety barriers will be needed.

Clearly, validation will be impacted by the controls approach so it must be considered an inherent part of Phase VII. If possible, obtain the executed protocols to serve as a reference for validating the new installation. Under traditional IQ/OQ protocols, chances are the existing protocols won't match your at-least-somewhat-modified control system or even your current qualification standards, but the information contained therein is worth its weight in gold by reducing time to rewrite documents as well as dramatically reducing the learning curve. Notwithstanding this, under the latest verification processes there may be some portions of the original documents that can be reused.

Phase VIII focuses upon the facility which will serve as the new home for the equipment. Here, most of the work involved layout and utility availability, but there can be unforeseen problems from seeming innocuous issues. As an example, while there may be adequate boiler capacity to support the thermal load of a new air handling unit, some plants only have low pressure steam. In order to provide the needed heat to the process, the original steam coil in such a case would be undersized and the chances are there is not enough extra space to accommodate a larger coil within the chassis of the air handler. A separate booster unit will resolve the thermodynamic issues, but the original space requirements will increase and the control software will have to be revised, along with the PID tuning. Relocating the air handler further from the process equipment may be required, which means yet more thermal load to make up for heat loss in the ductwork. Even if traced ductwork is utilized, the extra distance will increase the system's response time to calls for temperature change to the ultimate detriment of the process. Once again, the need for the user, OEM, and engineering company to function as a team and continually cross-check each other's design decisions is a critical success factor.

Facility Considerations

Equally important consideration should be given to the facility once prospective used equipment has been identified. An especially thorough analysis of the facility must be done to mitigate equipment installation and operational problems. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 2 – Oral Solid Dosage Forms* is an excellent resource related to equipment and facilities requirements. Risk Assessment as outlined in the Equipment Consideration Chapter also must include facility and utilities to provide a comprehensive picture to help determine if used equipment is truly the right choice. At a minimum, the following items should be reviewed:

Code Compliance

When new equipment is purchased, the specifications can be written to require compliance with the pertinent Code Requirements for the specific site. This is a significant benefit to the Owner because it places the risk of Code Compliance on the equipment supplier. Used equipment is purchased "as is," and often will require some level of modification to be in compliance.

Electrical components and related power supply systems (disconnects, starters, lighting, and wiring) are likely to have compliance issues. This is especially true if the operation requires special classification for explosion or fire hazards, which many OSD operations do. It is also likely if the original equipment was designed for use in a different country or if it is older equipment. In most locations, building codes require that new installations of old equipment must be brought up to compliance with current standards, and that can be an issue. These modifications can be complex and can become a major schedule obstacle.

Space Considerations

Speaking of space considerations, used equipment reduces your ability to customize the equipment to function well in your facility. In fact, the equipment is probably customized to work well in a different facility, which may not even be the

one it was installed in most recently. Panel locations, door swings, access panels, and maintenance access areas all must fit your application or be adapted to work. The adaptation could be minor or substantial and a deal killer.

Moving large equipment components into a space can sometimes be challenging, regardless of whether the equipment is new or used. But in many cases with restrictive access, new equipment can be customized to fit in the access corridor or equipment elevator, and thus make the logistics far easier. Likewise, lighter materials could be selected to not exceed existing structural capacities. In facilities with tight constraints on access and for the room where the equipment will ultimately be installed, the adaptability of customizable new equipment could enable the operation to work in a smaller footprint or more lightly constructed facility. The shape of coils and vessels can be adjusted to fit when new equipment is used. So used equipment might be less desirable when space and access is tight or the facility is of light construction.

Keep in mind that many operations in a pharmaceutical production space require adequate room to stage carts or equipment or to facilitate process operations. Used equipment has far less flexibility. Be careful to think through every step of the manufacturing process and consider whether the new component will be suitable. Again, this is of particular importance if available space is tight.

Explosion venting of used equipment may pose unique challenges. It may be impossible to install a fluid bed processor with an explosion vent inside the facility when there is no clear path for the explosion vent routing. Can explosion suppression be an option in this case? If yes, this means additional retrofit work, additional controls, time, and expenditures. New fluid bed processors, for example, can be specified with a pressure rating of 10 or 12 bar to contain the explosion without a need for an explosion vent.

It is important with any pharmaceutical equipment installation to generate a Checklist. Even if the Pre-Owned equipment may be purchased "as-is," the checklist can be used to outline what is needed. Then the project team can identify the gaps between what the equipment can do and what the end operation must do.

As a part of this verification, the team should confirm that all elements needed for fully functional operation are included/available and operable. It is highly likely that some pieces will be missing. Maintenance crews often swap out parts from a decommissioned unit for use in an operating unit, and the tracking of that change is not always recorded appropriately. Likewise, interconnecting parts between components may have been sold as a piece of the component that was formerly connected to yours. The earlier the missing pieces can be identified, the more time you will have to resolve the issue.

Similarly, a unit purchase from a site in Puerto Rico or Texas may be missing some essential components that you will need in your plant in Rhode Island. A freeze stat and a preheat coil will be absolutes in some climates, but never used in others. And even when the equipment is there, the design capacities must be checked to assure that the component will be adequate in the new climate or installation.

Utility Issues

Relative to utilities, there are a number of points to consider:

- Are the correct utilities available for the equipment? Remember, with new equipment the supplier is required to provide equipment that meet specifications. With used equipment, the owner is responsible. So a high degree of caution must be exercised to protect the client.
- Is the equipment supplied with 380 V motors, for example? Does the wiring meet local electric codes? Are the electri-

- Confirmation that all elements needed for fully functional operation are included/available and operable
  - Dealing with missing elements, for example, a freeze protection coil on an air handling unit moved from a subtropical location to, say, Minnesota.
  - Defining scope of work, what needs to be provided to complete a fully functioning installation?
- Utility Requirements Review
  - Are there right utilities for the equipment – is the right power available for equipment supplied with 380 V motors, for example?
  - Is steam pressure and capacity adequate to support equipment?
  - Is chilled water available at right temperature and flow?
  - Are water and steam pressures compatible with ratings on the equipment?
  - What additional measures are required to rectify utilities deficiencies – increased piping or additional generating capacity, transformers for different voltages, heat exchangers? Those will have impact on space which may or may not be available in the existing facility. Additional space translates into cost and additional project time.
- Space Considerations
  - Once all the pieces are there, will they fit in the space and allow for required operational interface? Door swings, control panels, and component service access?
  - Can the components be moved into the space? What needs to be done to move the components into the space? May be able to dictate equipment dimensions and specify the largest component dimensional limit if purchased new. Facility alteration may be required to move used equipment in.
  - Accommodate explosion vents. It may be impossible to install a fluid bed processor with an explosion vent inside the facility when there is no clear path for the explosion vent routing. Can explosion suppression be an option in this case? If yes, this means a retrofit work, additional controls, time and expenditure. New fluid bed processor can be specified with a rating of 10 or 12 bar to contain explosion without a need for an explosion vent.
  - Equipment access in particular coil pulls, access doors cannot always be easily accommodated.
- Code Assessment
  - What codes and standards does the installation area meet?
  - Electrical classification compliance with local codes. If equipment is brought in from abroad there will most likely be upgrades necessary, in particular if solvents are handled.
  - Vessel pressure rating must be verified if the vessel was build to standards different than ASME?
- Control Systems Integration
  - This is covered under equipment considerations.
- Engineering Implications
  - Engineering fee is often set as percentage of equipment cost. When used equipment is installed, engineering effort is significantly higher due to missing information, missing parts, incompatible utilities. Time and effort will of course be greater, and so will the cost. This is not always clear to the Owner when weighing pros and cons of installing used equipment at the project outset.

Figure 3. Refurbished equipment projects: engineering and design considerations.

cal components appropriately (i.e., National Electrical Manufacturers Association (NEMA) or similar) rated? Is adequate power at the required voltage available? Applications requiring hazard classification rated components would be a major issue that would be relatively most difficult to remedy.

- Is the steam pressure and capacity adequate to support the acquired component?
- Is cooling water available at the right temperatures, differential pressure, and flow rates? If not, coil replacements may be necessary to accommodate the deficiency and enable the required heat transfer. Coils installed under that scenario would likely be larger or have more rows and or fins to achieve the additional cooling capacity. Even if plenty of space and elevation is available, this may still be a deal breaker.
- Depending on the equipment configurations, cooling and dehumidification capacities may be impacted by design conditions at the installed location. Oversized cooling and/or dehumidification equipment may be adaptable although such modification would likely reduce operating efficiency. Undersized equipment could possibly be more problematic and would require more costly modifications.

Automation and Control Systems

Equipment automation and control issues were addressed in the previous section of this article, but the facility and site operations aspect of automation systems should be considered as well. Imposing dramatically different automation systems or operating philosophies into a site can be problematic for some facilities. Imposing such challenges could become a GMP issue if operators could potentially become confused between the systems or the procedures taking place in the facility.

A **Standardized Checklist** for refurbished equipment could be a major help and avoid unnecessary oversights as seen in Figure 3.

Conclusion

Improving access to medication through cost conscious decision making is paramount to pharmaceutical manufacturing. As consolidations in the pharmaceutical industry occur and more and more surplus equipment is realized within companies and on the market, the ability to use available pre-owned equipment to contain capital project costs (thereby reducing the impact of cost of goods on our products) is becoming more prominent, but there are additional risks. Before committing to relocating that old tablet press from the bone yard or buying a used piece of equipment from an equipment re-seller, pause a moment to consider the outcome; there are many aspects of re-commissioning equipment that must be considered prior to, during, and after the decision to re-commission to avoid the consequences of delay, increase costs, operational complexities, or even project failure. In the end, if one applies the principles embodied in this article, the nuances and special requirements of a pre-owned equipment project can be properly managed to a successful conclusion.

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This article presents how the U.S. Pharmacopeia (USP) works to ensure the quality of pharmaceuticals by preparing standards.

The U.S. Pharmacopeia (USP) Responds to Changing Needs of Pharmaceutical Manufacturing

by Anthony DeStefano, Antonio Hernandez-Cardoso, Kevin T. Moore, Tina Morris, Horacio Pappa, and Radhakrishna Tirumalai

As the pharmaceutical industry shows continued global expansion, manufacturers and regulators are faced with novel and complex challenges in ensuring the quality of ingredients and finished products. The stakes include both public health and corporate reputations. While it's difficult to quantify with precision, many estimates cite the volume of Active Pharmaceutical Ingredients (APIs) in drugs taken by Americans that are manufactured abroad at up to 80%.[1] China and India have emerged as the pharmaceutical powerhouses, but other up-and-coming sources of APIs include Brazil and Southeast Asia – and there are others. Manufacturers and regulators must deploy all available tools to safeguard quality and safety in the resulting elaborate and far-flung supply chains, and new approaches are required as well. Such approaches must respond to the changing realities of the industry, accommodating requirements ranging from cost, to multi-facility/company laboratory capabilities, to regulatory enforceability.

Pharmacopoeial approaches to help ensure the identity, strength, quality, and purity of medicines and their ingredients have long been a key element of the safety nets that protect the drug supply, along with ethical manufacturers and good regulatory structures. American consumers, patients, and practitioners expect safe and reliable medicines – as they have a right to. However, in recent years, distressing incidents have shaken that confidence, not the least of which was the 2007 to 2008 public health crisis involving heparin (a widely used blood thinner) that was deliberately adulterated with a less expensive substance for economic gain, resulting in adverse reactions and deaths. And there have been other damaging incidents.

The U.S. Pharmacopeial Convention, a nonprofit public standards-setting organization, has been developing and updating quality standards for medicines since 1820. With the passage of the Food, Drug, and Cosmetic Act in 1938, most USP standards became enforceable by the Food and Drug Administration (FDA), and have served drug manufacturers with specifications, methods, and procedures needed to help ensure the quality of their products and that support a regulatory framework for compliance. All medicines marketed in the United States must comply with relevant USP standards for identity, strength, quality, and purity, and USP standards also are used in more than 130 countries. As with any scientific endeavor, USP standards must undergo constant revision and updating to take advantage of developments in methodologies and technology. To that end, USP's volunteers – distinguished scientists, regulators, researchers, and public health officials from around the globe working in Expert Committees and other bodies – have been focused on updating USP quality standards, and this engagement with the industrial and regulatory communities helps keep USP's standards current and relevant.

Modernization

The dissemination of up-to-date scientific knowledge and the application of advanced analytical practices play important roles in the global manufacturing of good quality pharmaceuticals. The USP has undertaken a large-scale modernization of our standards so that they may better reflect current scientific thinking and practices and to fill information gaps where they might exist for some API and excipient standards. In parallel to the USP's efforts, the FDA has established a monograph

modernization task force that is assisting the USP in setting modernization priorities. In addition to developing standards for small-molecule drugs that dominate the pharmaceutical market, the USP also has been focused on novel approaches for creating standards that are useful for the manufacture of the growing array of complex biologics.

Broadly speaking, USP standards come in three forms: monographs, general chapters, and reference materials. Monographs are documentary standards (specifications) for individual drug substances or products. General chapters are documentary standards that are broadly applicable procedures and methods (required when referenced in monographs and numbered from 1 to 999) or informational (numbered from 1000 to 1999). Reference materials are physical samples against which manufacturers test their own materials. Documentary standards are made public in the USP's official compendia, most notably the *U.S. Pharmacopeia–National Formulary (USP–NF)*. While the USP's modernization activities span both individual monographs and general chapters (that are either called out in particular monographs or applied as specified in *General Notices* of the *USP–NF*), this article focuses on the USP's revisions of general chapters that may have an impact on manufacturers and regulators worldwide.

Validation, Verification, and Method Transfer

Validation and verification of analytical procedures both play critical roles in a manufacturer's quality control activities in the laboratory. While similar, these are applied for different purposes, and the USP is re-assessing its related guidelines in the *USP–NF*.

The *USP–NF* specifies in its *General Notices* section that only results obtained by methods and procedures in the compendia are conclusive.[2] For those wishing to use alternative methods and procedures, the *USP-NF* does provide guidance on validating non-compendial procedures. Validation demonstrates that the accuracy, sensitivity, precision, selectivity, etc., of an analytical procedure are suitable for its intended use.[3] For example, when working with aspirin in a tablet form with the intent to run an assay on the aspirin, the user who is not using a compendial method must first validate that the method being applied does, in fact, accurately and precisely measure the quantity of aspirin in the tablet form.

Verification, on the other hand, is the user's demonstration that an article is suitable to be analyzed using the method in the *USP–NF*.[4] Scientists applying procedures described in the *USP–NF* to a compendial article are not required to validate the accuracy and reliability of those procedures. However, a laboratory employing a USP procedure for the first time, for example, should verify that it performs as intended.

Closely related to validation and verification is the concept of method transfer. As with verification and validation, the transfer of a procedure associated with a method looks at suitability in a specific context.[5] Transfer refers to the documented process that qualifies a laboratory to use an analytical procedure that originated in another laboratory, ensuring that the results of the transferred method are reliable. Factors to be taken into consideration during method transfer include the procedural knowledge of the laboratory personnel receiving the method and their ability to perform that procedure as intended.

The USP has recently established a new Expert Panel on Validation, Verification, and Transfer of Analytical Procedures, the ultimate goal of which will be to generate proposals for the revision of three USP General Chapters: <1224> *Transfer of Analytical Procedures*; <1225> *Validation of Compendial Procedures*; and <1226> *Verification of Compendial Procedures*. Three new mandatory general chapters on spectroscopy also have been proposed:[6] <852> *Atomic Absorption Spectroscopy*; <854> *Mid-Infrared Spectroscopy*; and <857> *Ultraviolet-Visible Spectroscopy*. Each of these general chapters contains sections on validation and verification with specific acceptance criteria for accuracy, precision, and other performance characteristics. In this manner, the USP is attempting to establish a more precise definition of what is considered to be an acceptable alternative procedure.

Microbiology

As stated, some of the USP's general chapters can apply across many articles. For manufacturers, the extent of microbial contamination in a finished product must always be a consideration. The USP's Microbiology Expert Committee looks at microbial presence and absence in both sterile and non-sterile pharmaceutical products. Non-sterile drugs – such as oral solid dosage forms or syrups – allow for the presence of small amounts of microorganisms in their makeup. Sterile products, on the other hand – which include parenteral drugs – must be manufactured and handled to avoid any microbial presence, given that they are administered into the bloodstream. Microbial contamination in sterile drugs can result in disease and – in some cases – even death. While all products purported to be sterile have to meet the requirements of General Chapter <71> *Sterility Tests*, sterility assurance is gained only through the use of robust and validated sterilization processes.

The USP's General Information Chapter <1211> *Sterilization and Sterility Assurance of Compendial Articles* addresses general principles of sterility assurance as well as information on sterilization processes. The USP has responded to user and stakeholder feedback that greater detail is needed to address specific sterilization processes. With future revisions, <1211> will focus exclusively on sterility assurance, and the USP has initiated the development of several chapters – the <1229.x> series – dedicated to individual processes. General Chapter <1229> will serve as an overarching general chapter covering the general concepts of sterilization. To date, 11 more focused general chapters have been planned, out of which eight will focus on distinct processes for sterilization, how they are to be conducted, and what materials are most suitable for their use:

- <1229.1> *Steam Sterilization by Direct Contact*
- <1229.2> *Steam Sterilization of Aqueous Liquids*
- <1229.4> *Sterilizing Filtration of Liquids*
- <1229.6> *Chemical Sterilization*

- <1229.7> *Gaseous Sterilization*
- <1229.8> *Dry Heat Sterilization*
- <1229.10> *Radiation Sterilization*
- <1229.11> *Vapor Sterilization*

The other three general chapters in the 1229.x series will address areas related to these processes:

- <1229.3> *Monitoring of Bioburden*
- <1229.5> *Biological Indicators for Sterilization*
- <1229.9> *Physicochemical Integrators and Indicators for Sterilization*

Another major consideration for manufacturers with regard to microbial presence is contamination control. General Chapter <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments* has undergone a major revision and will become official in 2012. By changing the focus from evaluation of cleanrooms to key guidance that supports sterile pharmaceutical processing environments, revised General Chapter <1116> addresses ways to help eliminate microbial growth, particularly when introduced by human contact. Guidance in the general chapter as well as monitoring parameters for microbiological evaluation should be applied only to cleanrooms, Restricted-Access Barrier Systems (RABS) and isolators used for aseptic processing. Changes to <1116> include clarification of limitations of counting methods used in microbiological evaluation, including sampling, recovery, data tracking, and trend analysis. The general chapter provides an improved description of microbiological incubation conditions relative to intended recovery (e.g., typical temperature and time, or modification for slow growers). The general chapter also gives guidance on the establishment of sampling plans and sites; microbiological sampling methods (e.g., air sampling, surface sampling); contamination recovery rates, and other important microbiological control parameters.

In the arena of bioburden control for non-sterile pharmaceutical products, very little information is available either in the pharmacopoeias or regulatory guidance documents. Clearly, the quality of raw materials, the surrounding environment during manufacture, and personnel conducting quality control activities are just some of the factors that can contribute to the bioburden of a product. In a draft proposal that will be available for public comment in the USP's *Pharmacopeial Forum* in 2012, the USP will recommend a risk-based approach to bioburden control. By looking at factors that have the potential to affect product quality and patient safety and considering the best ways of addressing these, the user can then identify the risk associated with a product and apply appropriate methods for bioburden control. Points for consideration when assessing potential risk associated with non-sterile drug product manufacture include:

- synthesis, isolation, purification, package, and storage of drug substances
- inherent antimicrobial properties
- water activity
- equipment design and cleaning
- process water production, storage, distribution, and use
- route of administration
- age and general health of the patient population expected to use a drug product

In the case of antibiotics, microbial assays are used to measure a drug's potency by looking at its inhibitory effect on a target microorganism. Because of difficulties associated with conducting this type of assay and the time required for its completion (three to four weeks), the USP is exploring the use of a more rapid High-Performance Liquid Chromatography (HPLC) assay as a replacement. While not all antibiotics have an approved HPLC assay, the USP will look for guidance from its newly established Expert Panel on the topic to recommend validation criteria for replacement of an antibiotic microbial assay by HPLC methods. The USP also will look to manufacturers for information on validated HPLC methods that have been approved by regulators for inclusion in specific antibiotic monographs.

Similarly, current pharmacopoeial microbiology tests – such as sterility tests – rely on the demonstration of microorganism growth. Limitations of these tests include their low sensitivity as well their time- and labor-intensive nature. The USP is seeking to identify new referee tests or procedures (used by the FDA or a third party to assess regulatory compliance) based on modern methods that can detect and enumerate microorganisms in a more rapid and sensitive manner. The USP Microbiology Expert Committee also is working to update General Chapter <1223> *Validation of Alternative Microbiological Methods* to enable the user to validate microbiological methods, including those based on modern technologies.

Modern microbiological methods, the <1229> series of general chapters associated with sterilization, and USP efforts related to bioburden control in non-sterile products will be key areas of discussion at a USP workshop on microbiology quality standards scheduled for July 2012 at the USP headquarters in Rockville, Maryland, U.S. (http://www.usp.org/meetings-courses/workshops?).

Impurities in Drug Products

Another key area for the USP's standards modernization activities focuses on impurities in both Over-The-Counter (OTC) medicines and prescription products. The USP has established an Expert Panel in partnership with the FDA and the pharmaceutical industry to identify more modern scientific standards that can help ensure the appropriate control of organic impurities. There is a public and regulatory expectation that OTC products will be of comparable quality to prescription products, whether they are marketed under a USP monograph or one from the FDA. Although the USP monographs exist for all active ingredients covered in the FDA OTC monographs, the USP does not have monographs covering most of the drug combinations (drug products) that can be marketed under the FDA monographs, and the USP is working to acquire those currently missing from the *USP–NF*. Such OTCs are available in a wide variety of dosage forms,

colors, and flavors, which change frequently based on market demand and the large number of manufacturers worldwide that make them. All OTC drugs are subject to existing USP quality standards, and in the context of its overall modernization efforts, the USP has received a list of OTC priorities from the FDA, focusing first on acetaminophen and diphenhydramine as well as several inactive ingredients. Modernization of these monographs addresses quality gaps, such as missing or outdated tests for impurities (including degradation impurities) and the replacement of non-specific identification tests with more specific methods.

In a September 2011 workshop sponsored by the USP and the FDA, attendees explored some key quality challenges posed by OTCs. One critical factor is the large number of dosage forms associated with a single drug substance. For example, currently in the *USP–NF* there are 37 different monographs for acetaminophen dosage forms alone (acetaminophen is not covered by an FDA OTC monograph). The USP is looking at a number of novel approaches to help streamline the development of missing or outdated monographs. Future discussions with the FDA and industry stakeholders will help in establishing the optimal paths forward. General Chapter <1086> *Impurities in Drug Substances and Drug Products* includes key definitions associated with impurities that are aligned with those established by other pharmacopoeias and the International Conference on Harmonization Q3B (ICH Q3B) (the guidance for registration applications for the content and quality of impurities in drug products produced from chemically synthesized drug substances not previously registered in a region or a member state of ICH). Proposed revisions to General Chapter <1086> are being addressed by the USP, and could include general guidelines for the detection and qualification of organic impurities as well as a decision tree for use when needing to address or report impurities associated with manufacturing processes.

Today, some 400 monographs in the *USP–NF* are related to OTC drug products, and changes to General Chapter <1086> will be relevant to those as well as any new OTC monographs yet to be included in the USP's compendia. Additionally, the USP's Monograph Modernization list – accessible at http://www.usp.org/USPNF/submitMonograph/improveMon.html – comprises about 700 small molecule and excipient monographs out of approximately 2,600 eventually needing modernization, and input from stakeholders is strongly encouraged.

Identification Tests

In addition to exploring issues associated with the detection and measurement of impurities, the USP's General Chapter Chemical Analysis Expert Committee has been examining modernization needs related to identification tests in General Chapter <191>, *Identification Tests–General*. Recent adulteration issues with some pharmaceutical products have prompted the FDA to pay special attention to compliance with all identification tests since these are the first barrier against counterfeiting and contamination. Mentioned in hundreds of monographs, General Chapter <191> is one of the "top" most-referenced chapters in the *USP–NF*.

Traditionally, wet chemistry tests (e.g., color-based tests, such as acid-base, precipitation, or complex formation) and classic flame tests (complementary tests for sodium, potassium, calcium, copper, and lithium) have been the methods of choice for pharmaceutical product identification. Because these tests rely on users distinguishing such properties as color, they can be subjective. Among the 44 tests included in <191>, 19 currently include substances that are not suitable because of current environmental legislation or safety concerns (e.g., chloroform in bromide identification or mercurous nitrate in thiosulfate identification). Rather than reviewing the 44 tests one at a time for possible revision, the Expert Committee is taking a holistic approach to all tests included in the chapter and is exploring instrumentation procedures to replace traditional testing for identification.

Cognizant that not all manufacturers will adopt instrumentation approaches for identification, the USP asked manufacturers in 2011 about current user needs and practices. Of approximately 400 responses, the majority (92%) reported using wet chemistry for identification testing, but many of those who do so (64%) also use additional testing methods. For example, there is moderate use of atomic absorption (35%) and spectrophotometric methods (30%). Fewer use ion chromatography (22%) or inductively coupled plasma (19%). When asked to explain ways in which General Chapter <191> can be improved or modernized, nearly seven in ten respondents (68%) provided suggestions. The top suggestion focused on the addition of modern techniques or clarifying procedures. The top reason for favoring wet chemistry replacement was that alternative methods are more quantitative and less subjective, while the top reason for being opposed was instrument cost. Additionally, nearly one in five indicated that other methods should be alternative or optional. These and other results of the survey will help to shape the USP's thinking about future revisions to General Chapter <191>.

Biologics and Biotechnology

Another area of focused activity for the USP general chapters is large molecule products increasingly used to treat complicated disorders and diseases. Collectively referred to as "biologics," these products range from small peptides with simple structures to more complex mixtures such as vaccines. What they have in common is that they are manufactured using living material. The role of biologics in the therapeutic landscape has been rapidly expanding, as are, in consequence, critical issues associated with their quality assessment.

The USP's expanding portfolio of monographs and chapters for biologics increasingly uses a modular approach that involves vertical (product-specific), horizontal (general), and product-class standards. Due to the complexity of and variety among biologics, it is helpful to group these drugs into product classes based on their molecular make-up. Within a single molecule class, the same or at least similar analytical approaches often can be applied across multiple products. This "platform approach" applies to many classes of modern biologics, such as Monoclonal Antibodies (MAbs). Centered on shared quality attributes and testing expectations, these ap-

proaches can be captured in a general chapter. A USP Expert Panel has worked on General Chapter <1260> *Therapeutic Monoclonal Antibodies*, which provides a general overview of antibody therapeutics. In addition, the USP is developing a clearly defined set of quality expectations related to monoclonal antibodies in General Chapter <129> *Quality Attributes of Monoclonal Antibodies*. General Chapter <129> will be linked to other *USP–NF* general chapters that cover relevant analytical procedures as well as quality expectations for ancillary and process materials used in the manufacture of MAbs. It also will contain analytical procedures and acceptance criteria for monoclonal immunoglobulin (IgG) products. The Expert Panel working on the chapter will be conducting a round-robin study with broad industry participation to obtain stakeholder feedback on some of the proposed procedures, as well as collect batch data that will allow the USP to set meaningful specifications in the general chapter.

Clearly, common specifications will not be feasible for all procedures and quality attributes that define a monoclonal antibody product, and defining the analytical "common ground" among products represents a major challenge in this standard-setting effort. Based on the current thinking of the Expert Panel, common methods like Size-Exclusion Chromatography (SEC) for the detection of size variants, as well as Sodium Dodecyl Sulfate (SDS) capillary electrophoresis for purity, are the most promising candidates for platform methods with agreed-upon specifications. Much more challenging is the area of biological potency determination since this is unique to the mechanism of action for each individual antibody. Thus, this area will only lend itself to the development of general recommendations on how potency assays for MAbs should be approached. With this product-uniqueness in mind, class chapters are intended to link to individual product monographs that delineate the specific quality attributes of a given drug. However, given the complexity of biologics, it is critical that a broad foundation of general standards underpin the individual product monograph and set a more level bar for minimum quality expectations across a molecule class. Figure 1 illustrates the linkage between horizontal (general chapters) and vertical (monographs) standards for the example of monoclonal antibodies.

Other USP initiatives related to biologics include general chapters related to protein structure and post-translational modifications. General Chapter <1084> *Glycoprotein and Glycan Analysis–General Considerations* addresses modifications that result from the process of glycosylation, which adds to the complexity of characterizing biologic products. The general chapter is an analytical strategy document that uses decision tree diagrams to guide users through the analytical choices available to design product analysis in the spirit of ICH Q6B and based on molecule type. The ICH Q6B guidance document provides general principles for the setting and justification of specifications for biotechnological and biological products to support new marketing applications. Figure 2 shows one of these decision trees.

In addition to <1084> as an informational general chapter, the USP is working on two general chapters that contain procedures for oligosaccharide and monosaccharide analysis. These general chapters will be associated with physical refer-

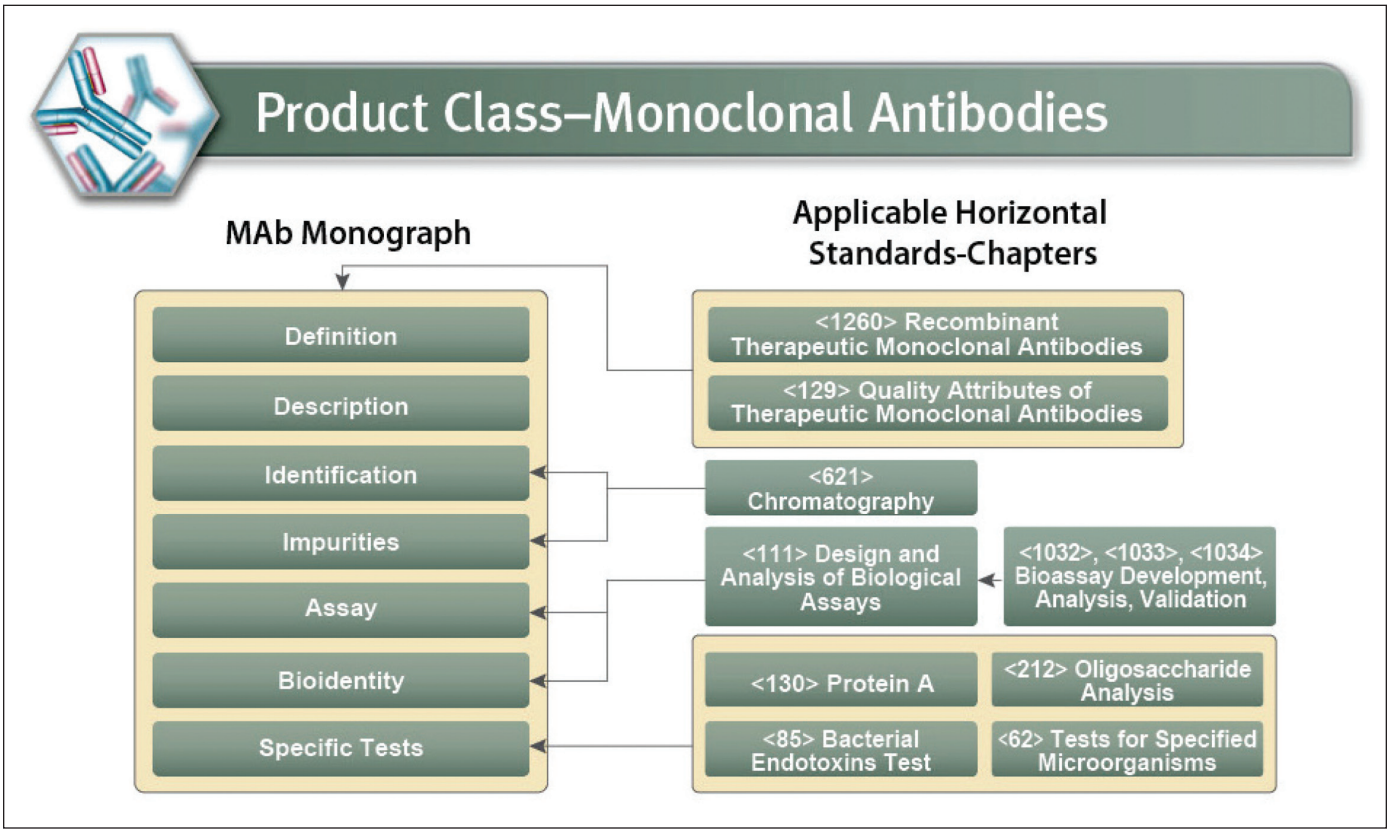

Figure 1. Linkage between horizontal (general chapters) and vertical (monographs) standards for the example of monoclonal antibodies. (Source: U.S. Pharmacopeia)

ence materials designed to aid in establishing and verifying system suitability during method development, qualification, and validation.

The potency assessment of a biologic is also a central quality consideration. Over the last several years, the USP has developed a comprehensive set of informational general chapters dedicated to bioassays. In addition to General Chapter <111> *Design and Analysis of Biological Assays*, which provides direction on creating appropriate strategies for biologic potency, the USP has completed a new suite of general chapters that includes guidance and information on the development, analysis, and validation of biologic assays. General Chapters <1032>, <1033>, and <1034> are scheduled to become official with the *First Supplement* to the *USP 35–NF 30* in August 2012.

Another key component of biologics manufacturing is the use of ancillary materials, such as growth factors and process enzymes, in the production of vaccines and cell- or tissue-based therapies. In general, these materials must be removed from the final product once the manufacturing process is complete. General Chapter <1024> *Bovine Serum* looks at quality issues related to the production, sourcing, and characterization of this group of ancillary materials along with risk-assessment and -mitigation measures associated with their use. In addition, General Chapter <90> *Fetal Bovine Serum–Quality Attributes and Functionality Tests* became official in the *USP–NF* in 2011. General Chapter <90> includes tests that determine the functionality of specific Fetal Bovine Serum (FBS) lots and aid in optimizing growth conditions of mammalian cell cultures in the presence of FBS.

Internationally Harmonized Chapters

As the discovery and manufacture of pharmaceutical products have become global endeavors, the pharmaceutical enterprise has looked for ways to minimize redundancies that impact regulatory and/or legal requirements for companies around the world and ultimately help to expedite delivery of medicines to patients. One activity that aids in overcoming such redundancies is the harmonization of standards by the Pharmacopoeial Discussion Group (PDG) – which consists of representation from the European Pharmacopoeia (EP), the Japanese Pharmacopoeia (JP), and the USP (the World Health Organization is an observer). Since its formation in 1989, the PDG has worked to eliminate or minimize industry's need to perform multiple tests and procedures and to comply with different countries' acceptance criteria for the same pharmaceutical article. Because excipients and general chapters affect a broad range of pharmaceutical articles, PDG's workplan has targeted 63

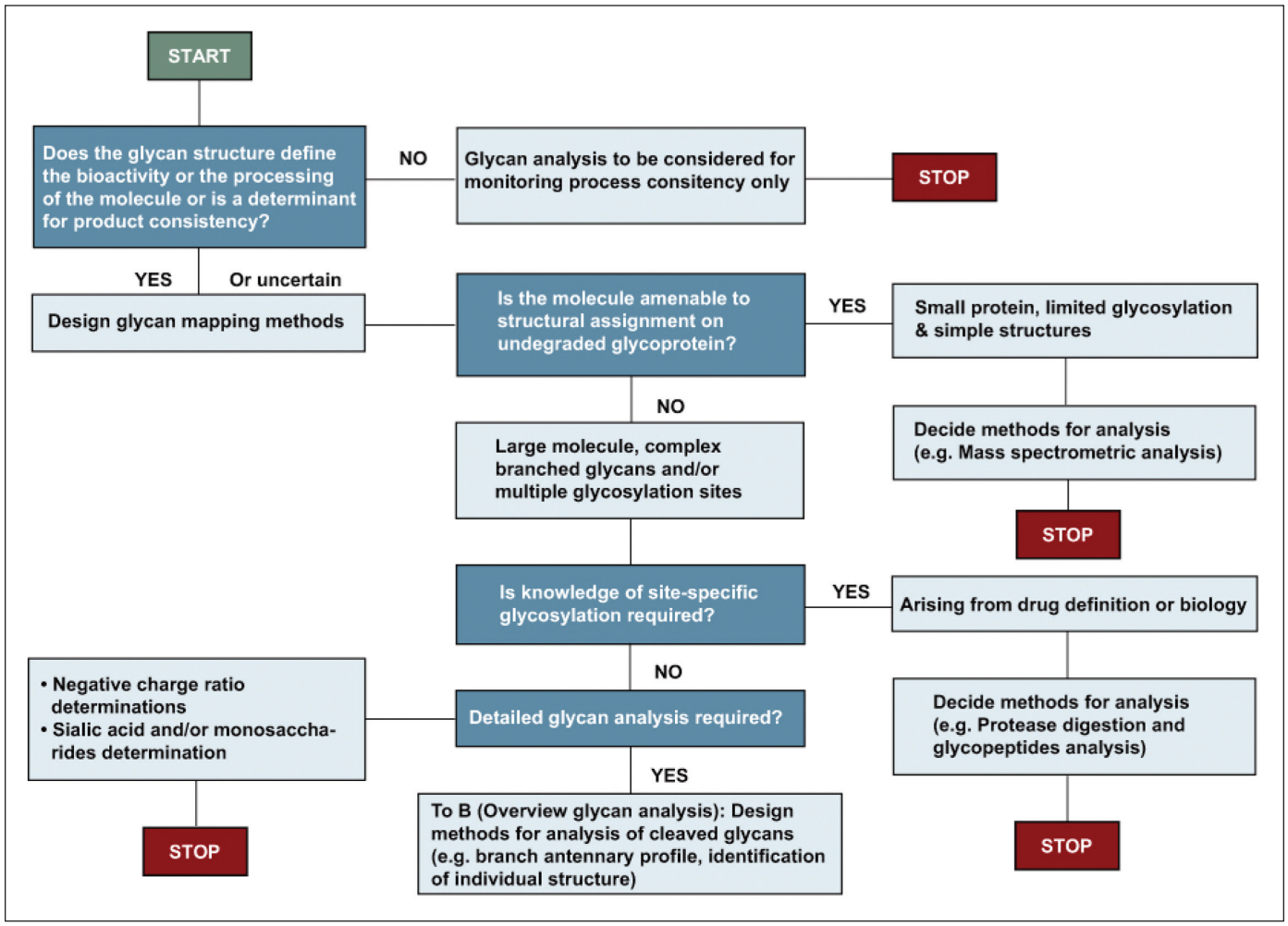

Figure 2. Decision tree diagram. (Source: U.S. Pharmacopeia)

excipients and 34 general chapters. Forty-one excipients and 27 general chapters have been harmonized to date.

Proposals for articles to be harmonized go through a public process similar to that in which the USP sets all standards, involving Expert Committee review and an open comment process. Overall, harmonization is a seven-stage process with PDG items being published at two stages – Stage 4 for "Official Inquiry" and Stage 6 for "Adoption." A coordinating pharmacopoeia takes the lead in drafting a proposal for an article to be harmonized and then shepherds it through the PDG process.

In the area of biotechnology products and biologics, six USP general chapters have been harmonized through PDG's collaborative efforts. Of those six, three are currently undergoing revisions: <1055> *Biotechnology-Derived Articles–Peptide Mapping*; <1056> *Biotechnology-Derived Articles–Polyacrylamide Gel Electrophoresis*; and <1057> *Biotechnology-Derived Articles–Total Protein Assay*. These three general chapters are at Stage 3, 3, and 2, respectively, in the PDG process. Among the general chapters mentioned in this article, portions of General Chapter <71> have been harmonized with the corresponding texts of the European and/or Japanese pharmacopoeias. Harmonized and non-harmonized (regionally-specific) texts are marked accordingly within the chapter for specificity.

Protecting Public Health – A Collaborative Effort

Keeping pace with the many changes in the pharmaceutical, regulatory, compendial, and technological sciences is no small effort. The USP relies on keeping its standards current through collaboration with industry, the FDA, and other regulators. As the manufacture, sourcing, distribution, and registration of pharmaceutical products are ever more global, collaboratively-created quality standards for medicines will continue to play a major role in the overall safety net designed to protect public health.

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PHARMACEUTICAL ENGINEERING Interviews

Dr. Aris Persidis, President and Co-founder, Biovista, Inc.

With patent expirations looming for many major pharmaceutical companies, drug repositioning has become a matter of intense interest during the past few years. Biovista's President and Co-founder discusses the basics of drug repositioning and the potential impact it could have on bringing new drugs to the market.

Dr. Aris Persidis is President and Co-founder of Biovista. He has also served as Senior Vice President at Upstate/Serologicals, Managing Director and President of RHeoGene, and Assistant Director-Medical School Technology Transfer Program and Assistant Professor (Adjunct) at the Entrepreneurial Center of the Wharton School of Business at the University of Pennsylvania (1993-1997). He also participated in the co-founding of Cellzome (Heidelberg, Germany) and Anadys (San Diego, CA). Dr. Persidis is a recipient of the Honeywell European Futurist Award (1986) and has published extensively on biobusiness subjects. In 1997-2000 he authored the monthly "Industry Trends" column for the journal Nature Biotechnology. He has published more than 80 papers and book chapters, has lectured at Wharton, the Columbia Business School, George Washington University and the University of Auckland Business School, and is a frequent speaker at major international meetings. Dr. Persidis holds a First Class B.Sc. Degree in biological chemistry from Essex University, U.K. (1983-1986), and a PhD in biochemistry from the University of Cambridge, U.K. (1986-1989).

Q What is your background and how was Biovista founded?

A I am a biology major with a PhD in biochemistry. Biovista was founded by Andreas Persidis, a PhD in artificial intelligence, and me. Initially, the company focused on business intelligence in the life sciences, offering insights from the analysis of business events. Over time, we felt that a number of ideas and solutions from that work could be applied to the problem of systematic discovery in drug development using scientific data and results as the basic resource. Based on this observation, we developed this aspect of our original technology to create our Clinical Outcomes Search Space (COSS™) platform. At its heart, this is a platform for systematic discoveries which in its current incarnation is being applied to the task of drug repositioning and drug risk profiling.

Q How would you define drug repositioning?

A Drug repositioning is the process of finding new uses for existing drugs. Viagra is a good example. Originally, it was being developed for pulmonary hypertension. During its clinical trials, some astute doctors observed a side effect that could help men with erectile dysfunction. Enter Viagra. Traditionally, drug repositioning targeted drugs that have already entered the market and in most cases are off patent. Recently, there has been a trend to proactively reposition compounds even before their patents expire, or even before they enter the market.

Q What is the current state of the drug repositioning market and in what direction do you see it heading in the near future?

A We consider drug repositioning to be a strongly emerging market. By simply looking at "soft" criteria, like the number of conferences and publications on the subject or the number of groups/companies entering the space, one can see a clear upward trend. But even more importantly, we are seeing increasing acceptance within large companies and other groups who just a few years ago were skeptics.

In terms of direction, we see three stages of evolution: in a first stage, repositioning will become a more systematic process, the aim being to fill the pipeline and ensure the appropriate exploitation of existing IP. In a second stage, repositioning will evolve towards the earlier phases of a drug's life cycle, increasingly being applied to compounds at their earlier development phases. In other words, it will become a part of a drug's life cycle management process. This will become very important as companies attempt to protect themselves from what we at Biovista call "competitor adjacency moves," which is nothing more than the "usurping" of IP estate from less than vigilant IP owners. Ultimately, we expect the opportunities for repositioning to have run their course and the need to discover novel chemistry and novel mechanisms-of-action (MoAs) will resurface. At that point, we expect that some of the tools and techniques developed for drug repositioning will be used for discovery of new chemical entities (NCEs), as well as for a better understanding of biology itself. At Biovista, we are already down this path by virtue of the way our COSS platform has been designed and set up.

We see that repositioning will be useful to the life sciences industry in three ways in the years to come: first, it will help develop new/better therapies to address medical needs, second, it will help us develop new techniques to make discoveries on a systematic basis and finally, as a consequence of the above, it will help make drug development more efficient. That is why we believe at Biovista, that if embraced and practiced correctly, drug repositioning has the potential to be a game changer for the life sciences industry.

Q What value is sought by pharmaceutical companies when they consider drug repositioning as a business strategy?

A We believe that pharmaceutical companies are looking for value at multiple levels when considering drug repositioning. An obvious value proposition is of course the re-valuing of "dormant assets" (i.e., the breathing of new life into assets that have been shelved for one reason or another). But, there is more to it than this. As I said before, when done on a systematic basis, repositioning can become a proactive endeavor, and so contribute in a big way to the process of life cycle management. Becoming the target of competitor adjacency moves cannot be a terribly fun place to be, especially if we are talking about assets that are still under patent protection. This is the case with Enbrel®, the Amgen anti-TNF drug that was repositioned by Bioassets Development Corporation (BDC), to Sciatica. BDC was subsequently bought by Cephalon and soon thereafter, by TEVA. What this incident tells us is that one can no longer feel safe and remain complacent even when it comes to assets still under patent protection. Strongly supported method-of-use patents can be granted to competitors forcing the original owner to either cede the specific area, or come to some arrangement with the owner of the repositioned drug.

There are additional variations to this theme. For example, as a result of past practices, there are a number of pharmaceuticals which, while seemingly own the application of a certain compound to a number of disease areas, in practice do not have "full possession," meaning they are not sure for which of these areas to further develop their asset. Repositioning for these "known" disease areas could help prioritize them for the drug owner.

At Biovista, we are also seeing an increasing interest from groups with whom we speak, for areas such as the OTC market. In this case, the basic idea is the same, namely developing new product applications. However, there is a twist. The twist is that in the OTC market, speed of development is paramount and so high speed and systematic repositioning, as practiced by Biovista, becomes an interesting approach.

Q What are some examples of successfully repositioned drugs?

A Thalidomide is a good example of serendipitous drug repurposing. In 1964, Jacob Sheskin in the University Hospital of Marseilles was out of options while trying to treat insomnia in a patient suffering from Erythema Nodosum Leprosum (ENL). In a desperate attempt, he used thalidomide, which he believed might be effective as a sedative. Not only did thalidomide allow the patient to sleep, but it healed his sores at the same time. This effect was corroborated in follow-up clinical trials, which established thalidomide as a primary treatment for ENL.

Sildenafil (Viagra), is another notorious example. It was originally developed as a drug for coronary artery disease, but was found in early clinical trials to not be particularly effective against angina. As a side effect; however, it could induce marked penile erections, which led to its use in erectile dysfunction.

Finasteride (Proscar), is another interesting example. Originally approved for the treatment of benign prostate hyperplasia, it was subsequently found to be effective against male pattern baldness.

Q What is Biovista's role in the drug repositioning market and what makes your approach unique?

A We feel that Biovista is definitely one of the thought leaders in drug repositioning helping to shape the market, define what is possible, and show what should be expected in terms of predictive accuracy and efficiency of this process. The Biovista approach car-

ries the least amount of biases (always a good thing in a discovery context) and can truly claim that "it leaves no stone unturned," helping ourselves and our collaborators zero in on good opportunities quickly and relatively cheaply.

In addition, our ability to talk to the risk side of any compound puts us in the unique position of being the only group that offers under the same roof a balanced assessment of any repositioning opportunity. The benefit of this ability is felt in downstream tasks, such as in the design of clinical trials and in patient cohort analysis. It effectively increases the "resolving power" of our approach, since we can accurately identify patient groups with a higher probability of risk of side effects, or conversely a better chance of responding favorably to the treatment. To date, our collaboration with the FDA on drug classes has given some very encouraging results which we hope will contribute to the formation of the "Adverse Event Prediction Initiative" currently being contemplated.

Q What are the main intellectual property issues with drug repositioning?

A Drug repositioning is protected by method-of-use patents. While not as strong as composition-of-matter patents, these provide sufficient protection to the owner to justify investment and the commercial pursuit of repositioned drugs. A typical concern with repositioned drugs is the purportedly increased threat of off-label use (OLU). There are two important considerations here: first, OLU is not specific to repositioned drugs. All drugs on the market are subject to OLU and so this is more of an issue for regulatory and other authorities to try and contain, even though in some cases it may not be possible or even desirable. Secondly, OLU can be discouraged in a number of ways, most important of which would be formulation and dosing. Both of these aspects of delivering cures for patients offer a fertile ground for innovation and competition and are areas where generics companies are strong and traditionally compete. For this reason, we expect that dexterity in drug repositioning will offer distinct competitive advantages in the increasingly crowded space where pharmaceutical and generics companies are now beginning to compete.

Q How has Biovista's technology been validated?

A From the very beginning, validation of our approach and platform had clearly been at the forefront of our thoughts as we were setting out to invest the company's resources in developing its own pipeline. We also felt that we needed to have some indication of the expected "predictive accuracy" of our approach since our collaborators would be making decisions involving significant amounts of resources based on our recommendations.

So, as a first step, we embarked on what is called a "retrospective prediction" analysis, whereby we made predictions based on a limited amount of historic data, and sought to see if these predictions would be born out by subsequent events. The "yardstick" we compared our predictions against were the 2007 abstracts of ASCO where companies traditionally present adverse events connected with their drugs. This study, which is one of the biggest of its kind, has shown that our COSS platform has a Receiver Operator Characteristics (ROC) value of 0.75. This is rather good and definitely in the commercially viable range for predictive systems. As a comparator, the ROC value of the PSA test for prostate cancer is only 0.67.

But clearly we've gone beyond this study. At the level of in vivo animal model tests, our approach has to date a success rate of 80% on the efficacy side. We are also working with our current collaborators to take the results further downstream and will be able to report results at those levels soon. In the risk side as well, we have had some very encouraging results through our collaboration with the FDA and again hope to be in a position to report these soon.

Q What is Biovista's approach to developing its own pipeline?

A Our first repositioning projects have been in the area of Central Nervous System (CNS). This is clearly an area of medical need, but also quite challenging from a drug development perspective. However, there is significant internal CNS expertise at Biovista and we felt it was appropriate to test our capabilities and platform in an area where we felt strongly. Having established this, Biovista now follows a more market focused approach, selecting therapeutic areas that offer certain advantages such as accelerated development path or insights and inroads to harder but larger disease areas. Ultimately, we are looking for a strategy that will lead to success stories, sooner rather than later. PE

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Resource Planning in QC Laboratories

by Rafi Maslaton

This article presents a methodology and approach to resource planning, including both analysts and instruments in QC laboratories.

Introduction

Every year when budget time comes, the pressure rises to cut costs, cut spending, and reduce staff; however, improvements in service level and throughput continue to be expected. Lean and Six Sigma in some cases fall short when it comes to QC labs mainly due to its complexity. The savings in packaging and manufacturing could not be matched by the quality operation which increases the pressure even further. The largest single expense item in the QC lab is labor (analysts/chemists), which are relatively high paid positions; therefore, it would be beneficial to use an advanced resource modeling tool to more accurately project the expected number of people needed in the QC lab to support the business based on a given forecast. Without the proper modeling tool, the lab could end up with either too many analysts, leading to cost increase or too few that leads to an increase in overtime, resulting in higher costs and additional stress. Scheduling for QC labs can be quite complex; both standards development and translation of the commercial and especially non-commercial forecast into QC samples. Furthermore, with the increased pressure on sites/labs consolidation, space also becomes a constraint, i.e., space for instrumentation, flows, etc. Despite the importance of the above, the modeling capabilities in the lab are very limited or non-existent. Often budgets are based on the senior manager's experience, estimates, using a factor of let's say 10% more than last year and occasionally the use of MS Excel, but not based on verified data driven models. This article is focused on the methodology and approach to build resources modeling, including both analysts and instruments in the QC labs. The proven approach and methodology for laboratories modeling described in this article is based on a resource planning and scheduling software solution (Smart-QC). This article contains examples of actual case studies and projects that have been successfully completed by one of the top three pharmaceutical, biotech, and generic companies that have embraced this methodology for their QC laboratories planning and scheduling. One of the key reasons why QC laboratories do not have advanced modeling tools is the complexity in both standards development and translation of the commercial and especially non-commercial forecast into QC demands. This is mainly an issue for raw materials and New Products Introductions (NPI) that is usually not well defined when it comes to QC and harder to estimate in terms of labor and instrument requirements. In addition to the operational significance of having accurate resource modeling and the financial aspects, resource modeling

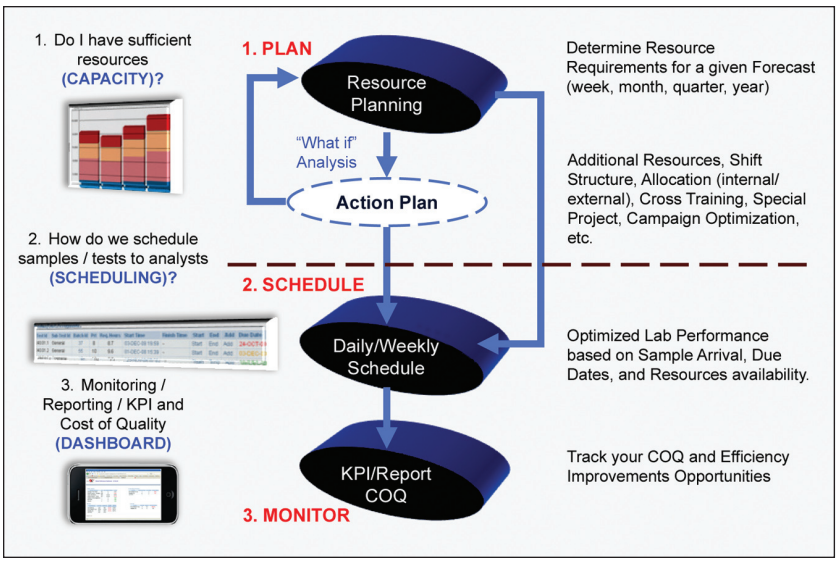

Figure 1. Managing labs operation: strategic level and daily operation.

could become a major compliance risk. As outlined in the Code of Federal Regulations (CFR) Title 21 (c) "…there shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product." This is applied to QC as well as other parts of the organization. For example, if the required QC resources are underestimated and significant pressure is applied on the QC personnel to get a timely release; that can lead to excessive overtime, which then leads to increase in stress level and eventually can result in human errors and a major compliance risk.[1]

Resource Planning: Instrument and Analyst in QC Laboratories

QC resource modeling is one of three major steps in managing lab operations. As can be seen in Figure 1, Step 1 is resource planning (the main focus of this article), which allows a company to determine if there are sufficient resources for both analysts and equipment to meet customer/business demands. There may be short term gaps that could be managed via over time, temporary work force, outside lab services. There may be more long term gaps that may require adding improvements in operational excellence, hiring, and/or outsourcing. Once the evaluation of resources is completed, Step 2 begins, which includes daily scheduling. This is the day to day lab operation scheduling effort performed primarily by the supervisor with lack of computerized solution. In Step 2, the incoming samples/tests are scheduled to the various analysts based on their qualifications, proficiency, experience level, availability, due date, priority, etc. Unlike Step 1 (resource planning), which is strategic level in managing the lab operations, this is the tactical level and requires a detailed and constant effort to schedule and maintain. Step 3 is reporting, which includes the development of Key Performance Indicators (KPI), dashboard, and overall monitoring of the lab performance. What is common to all steps is the data set required for the lab resource modeling that is the foundation for planning, scheduling, and reporting. This planning step (Step 1) presents even greater opportunities when dealing with multiple labs across multiple geography; being able to distribute some of the samples (i.e., stability) to other labs within the network to optimize the overall company supply chain and meet customers' (internal/external) demands.

How to Model the Lab Resource

As stated above, the strategic level of the lab's operation is resource planning and the first step in planning is resource modeling. The key in modeling QC environment is simplifying the labs complexity while maintaining the desired level of accuracy. Also critical is how to avoid falling into the trap of collecting data for 12 months via time studies and other time consuming techniques that usually do not lead to the expected results. The main area in terms of simplification is the test time standards collection and often throughout the industry, companies are making a huge investment in performing time studies and having few internal/external consultants running around with a stop watch collecting data. Due to the multi-tasking and concurrent activities in the labs, trying to perform time studies can be highly challenging. Unlike manufacturing, where for example, change over for a compression suite could take four to eight hours for two people and is a very similar flow for most products (minor/major); in the QC lab, most of the activities are short and varied between products/technique/instruments, so without proper grouping and upfront work as outlined in the methodology, a time study can be a major waste of effort and usually does not result in meaningful standards as expected. Once the methodology outlined in the next paragraph is followed, a targeted time study for activities that are time consuming and frequent could take place in an effort to streamline these processes and improve overall efficiency.

Table A presents the key steps to effectively collect standards (data) for the lab which are the foundation for resource modeling. Companies that have followed the process described in this article to obtain the data in Table A managed to collect the required information effectively and in a timely manner. The following are some of the key steps to initiate this process of data collection:

1. Develop list of products/raw materials and identify product/material families for all products in the lab. (LIMS/ERP should be the source.)
2. Identify representative product/material from each product family.
3. Generate bills of test for each representative product/material.

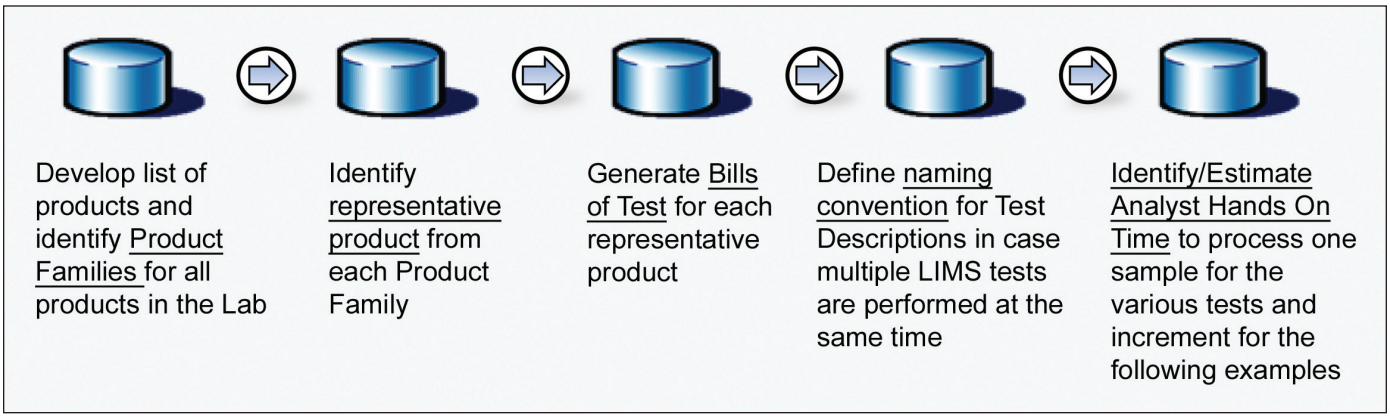

Figure 2. Data collection approach.

Product List	Includes list of ALL active products, their material/product code and their description. This list could be obtained from LIMS/ERP. In some cases QC may use a different product ID, yet it is critical to link between the ERP and the resource modeling to be able to translate the sales forecast into samples arrival.
Tests List	List of all tests performed in the Lab usually obtained from LIMS.
Product Test	This table creates the relation between the product and its associated tests. This table needs to include the stage of the product, which defines the form in which this product arrives to the Lab i.e., In Process, Finish Good, Stability. Each of these forms has different tests and stability has a different forecast as well.
Standard Groups	This is one of the key pieces in the approach to simplify the data collection approach. Instead of collecting standard for each test, we define test group that indicates the Hands On Time (HOT) is similar/same for a given method. For example, we have numerous HPLC tests yet many of them require the same level of effort in terms of sample preparation, setting up the instrument, analyzing the results and performing the audit/document review, hence there is no need to have dozens standards for each test, we could develop few test groups and associate tests to these groups. This is KEY in simplification of the data collection effort since it reduces the number of standards needed by 60-80%. Furthermore, in case of using actual time studies to obtain data, it provides a much larger option to collect data by GROUP vs. by each individual test. So we do not need to see ALL the tests for a given product several times which may take a long time to receive all multiple samples of the same product. Instead, we can observe the HPLC for product A and GC for product B and Physical testing of product C if these are using the same test group for each method.

Table A. Key steps to initiate process of data collection.

4. Define naming convention for test descriptions in case multiple LIMS tests are performed at the same time (could be consolidated and renamed).
5. Identify/estimate analyst Hands on Time (HOT) to process one sample for the various tests and increment HOT for the following samples.

This section outlines the detailed methodology for the data collection.

A. Identify product families for all products in the lab.
   1. Develop a product/material list. (LIMS/ERP should be the source.)
   2. Define potential product/material families based on similarities in testing, product/material name and strength, etc.
   3. Identify a product/material family for each product/material in the product material list.

B. Identify representative product from each product family. (This is to simplify the overall data collection process.)
   1. Review list of products/materials in each family for similarities and differences in products in terms of testing.
   2. Identify one product/material that has most of the tests performed for all products/materials in that family to be the representative of the family.

C. Define naming convention for test descriptions.
   1. Identify test descriptions that will provide adequate information on the type of test to the analysts when reviewing the developed standards:
      - Dissolution-UV and Dissolution-HPLC versus Dissolution only
      - Assay-HPLC and Assay-UPLC versus Assay only
      - Identification A, Identification B, Identification C versus Identification only (e.g., same product may have multiple ID tests).
      - Assay and Description versus Assay only if it is preferred to perform both tests together by the same analyst. (Revised test description for combined tests column is used to identify these.)
   2. Similar examples can exist for Assay and CU, Assay/Degradant, and Assay/Impurity.

D. Generate bills of test for each representative product.
   1. Using the representative product/material identified for each family, the laboratory product/material test specification, and the test naming rules defined in step C, generates the product/material-test relationships. (LIMS to be the source if available.)
   2. Include and mark the tests performed for release/finished product samples.
   3. Include and mark the tests performed for stability samples.
   4. Include and mark the tests performed for in process samples.
   5. Include and mark tests performed for full raw material testing vs. reduced testing.

E. Identify/estimate analyst hands on time to process one sample for the various tests.
   1. For each type of test, identify/estimate the total hands on time required by analyst to 1. prepare the sample, 2. set-up the instrument, 3. monitor/operate the instrument run, 4. perform post-run analysis and calculations, and 5. audit the results if applicable for a one sample run (Table A).
   2. The time should include only the hands on time spent by the analyst and exclude instrument time, e.g., HPLC may run for 10 hours, but the analyst may only be monitoring/checking the run hands on for 30 minutes during that time.
   3. For each of these tests, add the increment time required to test additional samples (i.e., one test would take six hours to perform all the HOT and any additional sample with the same test/method added would take an additional one hour vs. the six hours).

Table B examples are suggested definitions for the various key steps in performing a test. Each of the categories in Table B are further broken down to first sample and incremental (for each additional sample) components to enable campaigning analysis.

Sample Prep	Activities associated with the preparation of test related samples:
	• Dissolution, dilution, extraction, or other processing required by the test method on the samples • Setting up the lab bench / workspace • Media preparation, reagent preparation, buffer preparation • Mobile phase preparation and Standard preparation • Labeling samples • Documentation and LIMS / Other system
Set Up	Activities associated with the set up of the test instrument:
	• Conditioning or setup of instruments prior starting a test • Locate, retrieve or prepare required testing resources (e.g. specs, notebooks, Logbooks, HPLC column etc) • Retrieve samples, pre-made standards, buffers, reagents, media • Documentation / LIMS / Other system logging related samples or test resources
Run	Activities associated with the execution of a test method. Required HOT spent during the test run, for example:
	• Watch titration process until end-point is reached • PH meter is applied measure the PH reading of a sample • Taking a sample plate instrument reading • Watching the standards through the beginning of a HPLC run etc • Documentation during test method (Data Recording) • Required monitoring / observation time
Post Run	Activities associated with the conclusion of the test run related to recording / processing analysis of results data:
	• Data related activities after run completion (transfer, logging, trending, etc.) • Data analysis, calculations and spreadsheets • Results interpretation, reports and documentations, LIMS entry • Laboratory notebook, archiving original data • Cleaning the instrument and workspace used
Audit	Activities associated with the review of test results:
	• Including reviewing test, peer review, paperwork and LIMS / Other system approval

Table B. Sample components.

The sample components breakdown as can be seen in Figure 3 have more than 8,000 hours yearly for Team-1 alone that accounts for 35% of the overall work load to perform sample preparation activities. Improvement initiatives in this area could have a major return.

The same approach is applicable for modeling instruments capacity as well. This would involve grouping by instrument type/runtime and data collection for the first sample and the increment (i.e., injection time) for additional samples. Instruments up time (excludes calibration, preventive, and

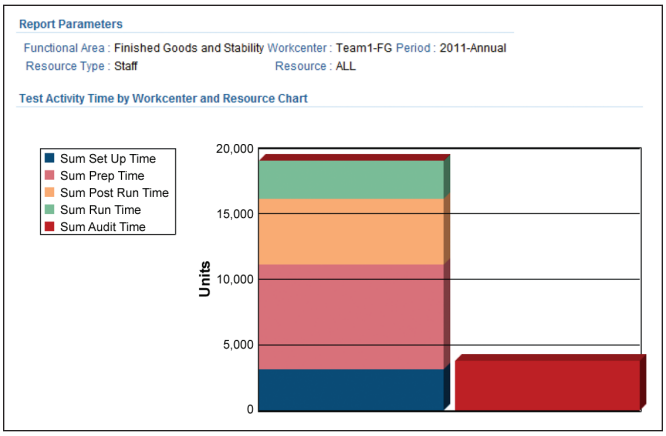

Figure 3. Sample components breakdown.

corrective maintenance) will be collected as well. Although our main focus throughout the article was the analysts, it is not uncommon that instruments can become a lab constraint for reasons such as limited space, cost, etc.

Other key information for the lab modeling is the analyst activities outside the bench work. It is a common challenge to communicate the activities that are not directly tests in the lab. The terms non-test activities and resource unavailable time for these activities will be used throughout the article. In other words, there is unavailable time due to vacation, training, meetings, holidays, sick days, etc., and also there are activities (non-test) such as data monitoring/trending, document creation/revisions, equipment qualification, general cleaning, glassware, GMP checks, instrument calibration verification, instrument troubleshooting, investigations, method transfer, method troubleshooting, method validation, special projects, and more. It is important to note that the above activities typically consume on average 30% of the analyst time. For example, if 42 analysts need to complete all the required testing in the lab, 60 analysts need to be hired to account for the non-test and unavailable time (42/70% = 60). Hence, it is critical to have a detailed list of activities, identify their frequency, the number of hours required per event, and to aggregate these to the percent of total analyst time.

For example:

- Assumption: two weeks of shutdown
- Two weeks for vacation; two weeks for GMP/EHS training, meetings, SOP, one week for holidays, one week for personal days, etc.
- On average, six weeks are spent toward non-test categories (i.e., calibration, method transfer, investigation).
- Then, in this case, excluding breaks/lunches, there are the following available hours per year:

52 (weeks per year) *37.5 (7.5 hours per day excluding breaks * 5 days per week etc.) – 14 (weeks per year that analyst is unavailable for testing)*37.5 = 1,425 hours per year out of 1,950 potential hours which represents ~ 73% availability for bench work (testing)

Once all the data collection effort is completed, the QC team should use historical data to verify the model results. For example, data collected in the past three to six months from samples processed in the lab can be used. These samples will be input to the model as forecast and running the calculation on these samples will provide the required number of analysts/instruments for that period. If this number projected by the model matches within +/-10 percent to the actual number of resources we had during this period, it can then be considered the "as is." At this point, we can use the model for future projection and declare the lab resources have been successfully modeled; however, it is crucial to incorporate the overtime, vacations, etc., during this period. These should be added/subtracted from the number of resources for the period compared; for example, if we had experienced 20% overtime during this period, we should normalize the resources by the same factor. If the number is too high, the estimates were too generous in the

standards or certain activities were double counted and it will need to be reviewed/investigated. The other extreme could be in the same way the need for 40 analysts was estimated for the last three to six months, yet there are 80 in the lab, so this means the estimates were too aggressive or some of the activities that are performed in the lab were missed. Once it is established within +/-10% that the model reflects the "as is," this could be the baseline for the lab model. As mentioned at the beginning, if the lab would like to perform a time study, once the grouping is completed and the forecast is entered, the time study could focus on the biggest hits, the highest contributing tests to the overall staffing/instrument requirements. Without these steps listed before, any time study may be focused on insignificant test methods and the value as a result will be limited.

When looking at the complexity and the significant effort required for building a resource model tool, one might question the benefits from such a model other than estimating the number of analysts and instruments needed for the QC lab.

Although it is important enough as it stands by itself, there are many other benefits that are part of this effort and help identify opportunities for improvements and help refine some of the operating model companies have become accustomed to use:

- Identify tests methods that contribute most of the HOT/FTE and work on improving these.
- Identify desired campaign size method/product and work with the supply chain and manufacturing on alignment/synergy to improve the lab efficiency. (For example, allow the lab to hold a sample for three days before starting with the testing so other samples could arrive to enhance the campaign size.)
- Establish campaign size target for the analyst based on the data collected - *Figure 4*.
- Estimate work load for a given period and re-prioritize projects/initiatives in the lab to meet the desired service level for the expected demand.
- Leverage the collected standards for scheduling, costing, and efficiency calculation.
- Identify ROI for projects leveraging the standards that were collected as part of the resource modeling.
- Define training road map based on Hands on Time (HOT) requirements for each method.
- Limit vacations during a specific period where demand exceeds capacity.
- In case of multiple sites, the application of resource modeling could branch into lab consolidation (i.e., centralized stability), enhanced redundancies and more, yet it requires the relevant and accurate information to make these significant decisions.

These are some examples where detailed resource modeling can be used and adds significant value to the QC laboratories and easily justify the level of effort required to establish such a model. Needless to say that any costing analysis, scheduling tool, and operational excellence initiative will need the same data as the resource modeling does. This is the foundation for any improvement program that involves the laboratories operation and should be carefully and methodically performed.

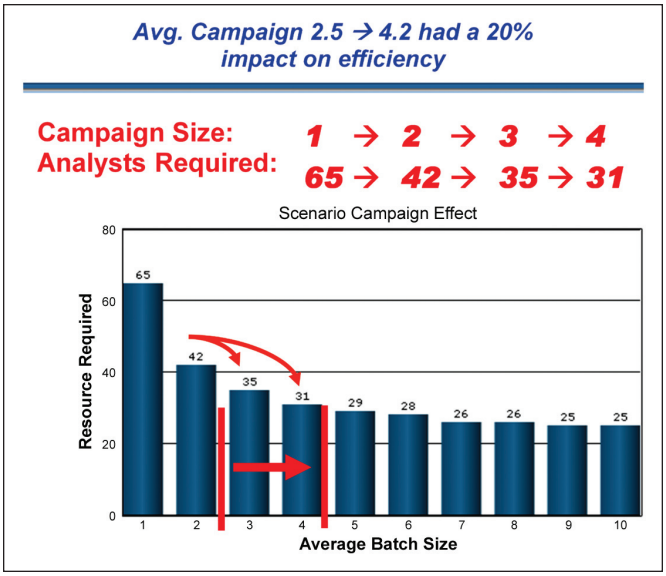

Figure 4. Campaigning effect on lab resources.

Figure 4 describes the affect of campaigning (batching) on overall resource requirements. In case of testing one sample at the time, the required resources will be 65 to accommodate the overall work required while campaigning three samples at the time could drop the overall resource level to 35 analysts.

The discussion above demonstrated how to model the QC lab resources and the importance of resource modeling when reviewing the key building blocks as seen in Figure 5 of QC operational excellence. From the top bottom, the essential piece of meaningful Key Performance Indicators (KPIs) is good standards. To determine the lab structure, the staffing requirements by function, by value stream, by team, by

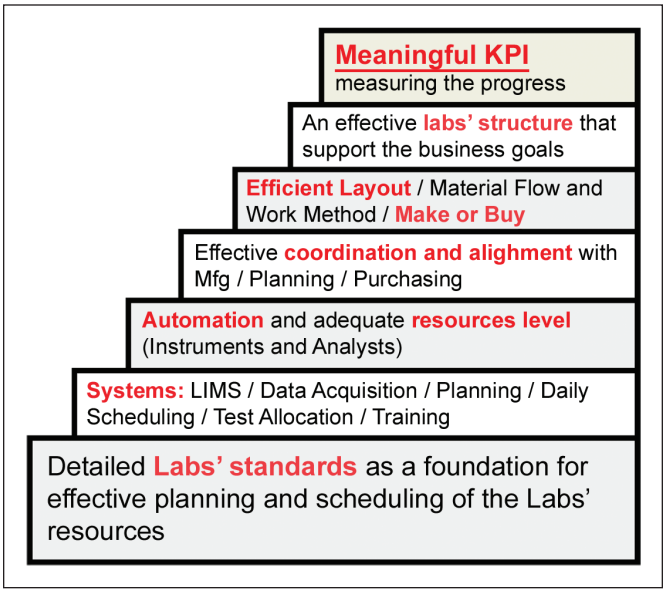

Figure 5. Operational excellence building blocks QC lab.

technology, and by center of excellence need to be identified. Furthermore, key output of a resource model that could affect the lab structure is the ability to match the current lab's personnel skill set (qualifications) vs. future needs. You might have the right number of analysts, yet you may not have them qualified on the right methods/techniques. The modeling tool can outline the required analysts by methods and could compare these results to the current lab skill set and establish a road map for training to close the identified gaps. Make or buy decisions should be based on factual data in case there is an alternative to test in house vs. using outside lab services. Coordination with planning should be based on modeled capabilities vs. opinion as it affects lab's service level as on-time delivery and turnaround time; these KPIs are highly affected by having the right size lab in terms of analysts and instruments; automation decisions should be once again based on factual data that will help determine the Return on Investment (ROI) of these projects. Any scheduling system will require the lab standards that are the foundation for effective planning model.

Summary

QC laboratories are one of the most complicated environments to model especially in labs that have high product mix, diversified products that are tested with a large number of analysts and instruments. In order to manage that complexity, a robust approach is required to simplify the lab complexity and also minimize the level of effort while maintaining accuracy of the model's inputs so decisions can be made based on that analysis. Resource analysis should be done on a regular basis, i.e., every month, quarterly, etc., based on the dynamics of the forecast. At this point, the lab should determine if there is a major change in required analysts or whether the incoming demand can be managed with the current resources. The criticality of modeling tool in today's economy is high since companies are trying to balance between cost and service level. Not having the correct information could lead to the wrong decision affecting either the cost of quality or with insufficient resources, the service level, and potential delays to launch new products as it takes several months to hire and train new analysts or to purchase, install, and validate new instruments.

The last key driver for having a resource modeling tool is to avoid a compliance risk; lack of adequate resources due to poor planning could lead to increase in employees' stress, increase in overtime, and eventually lead to human errors and compliance risk.

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This article presents the case that fault tree analysis is the better risk analysis method to apply early in software development projects.

Applying Fault Tree Analysis (FTA) as a Top Level Risk Management Tool in Software Development

by Paul Noble, PhD

Introduction

With the introduction of GAMP® 5, "A Risk-Based Approach to Compliant GxP Computerized Systems,"[1] in 2008, risk assessment is to be included in all life cycle phases of a computerized system. Conceived was "an iterative process used throughout the entire computerized system life cycle." Typically, this has been interpreted by the application of an initial risk identification followed by use of the popular FMEA method for determining the testing scope of software features.

Recently, it has been recognized in the Quality Risk Management (QRM) approach[2] that selection and exclusive use of a single risk management tool, such as FMEA, may limit the usefulness of QRM. The same limitation also can be expected when using risk management in a software development project. When the selection process in the referenced article is followed for risk assessment of undesirable events arising from software use, particularly during the early phases of a development project, the Fault Tree Analysis (FTA) method is suggested as one of the methods of choice.

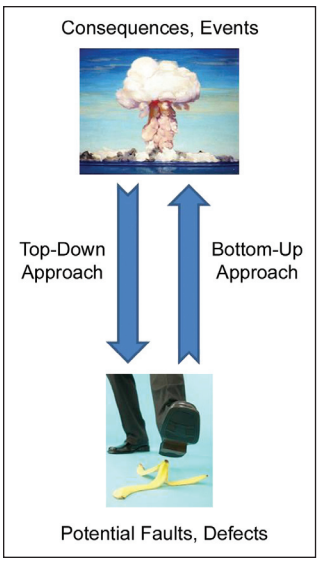

Figure 1. Risk assessment approaches.

FTA is a top-down type of analysis to be explained later. This article presents the case that it has advantages for the conceptual and design lifecycle phases. The distinction between top-down and bottom-up assessment methods has been largely ignored by the regulators, which leaves it to the project team to recognize the benefits of these two fundamentally different approaches.

The automation of business processes is targeted as an area for application of top-down methods, because potential human errors are a great source of risks for these processes, and such errors need to be addressed early in the life cycle of the system.

Unacceptable operation of computerized systems can arise both from human use and hard-/software defects. Human error has commonly not received the same attention in the past, while computers were replacing manual, error-prone operations. Where full automation is not practical, restriction of authorized use has been commonly relied upon to address the potential of human error, but this tactic is limited for automated business processes, such that they still commonly have a high potential for human error.

Although it is generally recognized that software defects and human errors are difficult to predict, and quantification of risks arising from them cannot be based upon failure rates, it may not be commonly recognized that they have different statistical dependencies. In tandem with the examination of a top-down approach to risk assessment, attention will be brought to the reader of the statistical nature of user errors, borrowing upon the statistical concepts of the QbD approach.[3]

Design Spaces Applicable to a Business Process

It is obvious that a business process cannot be controlled like a physical process can, even when the process is computerized. Active participants include both the users and the business players who participate in the process. Whereas a physical process can be controlled, such that it becomes robust and reproducible, a business process is not necessarily reproducible and is biased by the behavior of the active participants. Also, a physical process is governed by physical laws, whereas a computerized business process is partly governed by program logic, which can be in error.

In the QbD concept for physical (pharmaceutical) processes,[2] a design space is defined as, "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality." In physical terms, it is defined by the control parameters and their limits, which are needed to keep the process within a pre-defined quality level for the dependent variables, i.e., a desired event space. Of course, real systems have variability which cannot be completely removed and statistical methods are at the forefront of QbD. Typically, a physical process has several degrees of freedom, leading to multiple control variables, and the potential event space is quite large and usually considered mathematically to be infinite.

Conceptually, there is clearly a need for a business process to stay within a design space. Although a design space for program logic may not be a useful concept to employ, a design space which limits the human inputs to the system is. Inputs from other systems or devices can, as a useful simplification, be ignored because they are more reliable (assuming that the computerized system will be correctly specified and tested). It should become evident in this article that the separate consideration of user inputs has advantages in the design and review of the system.

The goal during the design of a computerized business process should be to limit the user inputs to the extent necessary for achieving the quality objectives. Users generally are not keen on limiting their freedom in use of the system, but experienced developers know that this must be done in order to create a robust product. Typical programming methods include selection lists, required fields, and the cancel button.

The problem of defining a design space for user input to a computerized business process may seem intractable, because so many possible inputs are involved. The data within a computerized system is still limited and digitized, such that at least we can think of a finite limit to the possible event space of user inputs. In this article, the computerized business process is considered statistically to be a finite system with a finite limit to the number of combinations of inputs.

Simplification is achieved by breaking the process down into individual steps within a process (as done with process modeling), and to consider inputs of individual steps at first independently. Further, the user event space can be further simplified by classifying user input to be one of three basic possible events:

- user makes no input (e.g., optional field, function not initiated)
- user makes incorrect input
- user makes correct input (to meet quality objectives)

Even with this simplification, the number of possible combinations of user inputs is usually large. For example, during the design of an entry screen, it may be planned to have m required fields and n optional fields, leading to a total of $m+n$ independent variables within this screen. The total number of possible combinations of inputs (user event space) is 2^m3^n. For a modest screen entry of three required fields and three optional fields, this number is 216, which can be employed as the statistical event space. The design space includes only eight members (which includes all correct combinations of optional fields).

A typical screen for material master data maintenance has about 20 data entry fields, for which circa three are typically required fields and the rest optional. The user event space for data entry in a typical screen is then $2^3*3^{17} \approx 10^9$, for which the design space is still large, ($1^3*2^{17} \approx 10^5$) because of the large number of optional fields. Material master data maintenance typically requires about a dozen such screens, such that in practice, very large event spaces are tolerated. The tricks to tolerance include extensive user training and experience, coupled with limited access and heavy reliance upon input restrictions and checks.

Still with such large event spaces, false inputs from users are inevitable, thus degrading the quality of the system data and performance. Recognition of the large potential for user error during design review could help balance the desire of users for optional fields, multiple selections, and fine granularity in data acquisition. As we all know, such desires are not deterred by cost factors. During the design, a limit should be set for the maximum event space of a user interaction (based upon experience).

Quality Risk Management (QRM) Methods for Design of Computer Systems

ICH Q9[4] describes a number of acceptable risk analysis methods for which the Failure Mode Effects Analysis (FMEA) is the most popular for identifying potential failures of a computer system, so that testing can be planned. FMEA is a bottom-up-analysis which starts with single component failures and yields estimations of their impact upon the system. Because it requires as a basis the specification of those components, it has limited usefulness when applied early in a project (iteratively throughout the lifecycle, as suggested in GAMP 5[1]). Risk analyses focused upon single component failures tend to miss the big picture, and usually are formulated by the solution provider. Risks caused by users typically receive scant attention.

Often the only risk management documentation available early in a project consists of a GxP assessment of the system or process. Although such assessments are useful for projects, they cannot substitute for a recognized QRM method. The only risk-based decisions obtainable from such an assess-

ment determine the scope of compliance documentation, e.g., validation documentation.

Fault Tree Analysis (FTA)[5] is a top-down analysis which starts with top undesirable conditions which should be conceivable early in the design phase. FTA is not commonly used in software development and the distinctions top-down and bottom-up are also not commonly known so that some explanation can be helpful here.

In the bottom-up FMEA analysis, one starts with an initiating event or fault, typically a software defect, and estimates its impact (consequences). The defect is a potential root cause for an undesirable event. Potential software defects are identified by examination of the software, and the FMEA is useful for risk ranking these potential defects based upon their probabilities and potential consequences. Although FMEA usually yields Risk Priority Numbers (RPN), the ISO standard[5] also recognizes qualitative approaches, i.e., simple rankings with this method.

By contrast FTA is useful when the potential initiating defects are not easy to identify, such as combinations of user errors. Here one starts with unacceptable top events and attempts to identify potential initiating events which can lead to them. It is thereby a top-down analysis. Where data is available, such as with mechanical systems, probabilities also can be associated with the defects, as with the FMEA method, and probabilities for the top events can be estimated. This is clearly not feasible for user errors. The ISO standard[5] also recognizes qualitative approaches using the FTA method.

Figure 1 illustrates conceptually the differences between the risk assessment approaches in terms of consequences and faults.

In the early design stages, the business requirements and a conceptual software solution are available, from which a top-down analysis can be started. The analysis leads to the identification of defects or errors which can lead to a top event. FTA allows analysis of multiple errors, which certainly need to be considered where multiple user inputs are involved. Attention should be given to potential human error before a design is completed, such that the design can be intelligently reviewed, and the future users of the system can be informed of what needs to be addressed in training.

For automation projects having little direct human interaction, an early FTA application can still identify critical software modules or functions to be targeted for a risk-based approach to qualification. It could replace the typical project GxP assessments with the advantage that the potential impacts, i.e., top events, are also identified and associated with the software components.

In summary, utility is seen for an early application of FTA to identify primary risks, particularly for business processes, in order to improve the design of the user interface. Critical software modules identified during the top-down analysis can later be targeted for a bottom-up analysis. Risks associated with SW defects, which can only be fully appraised when the specifications are available, may be best analyzed via a bottom-up analysis later in the project so that risk ranking can be assigned.

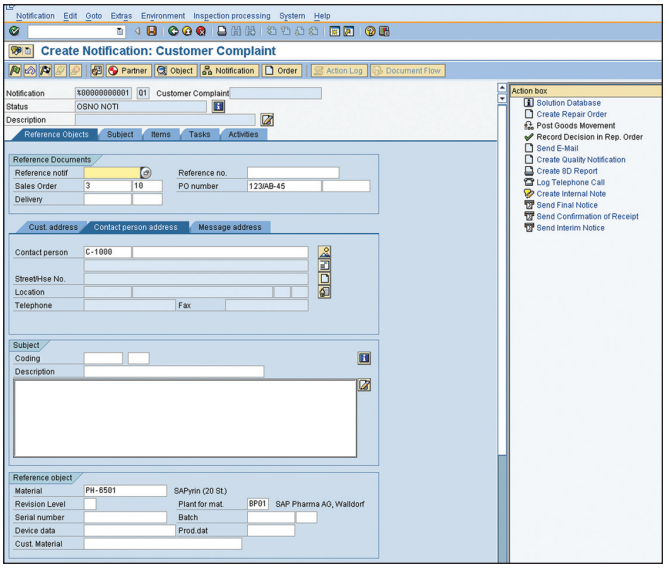

Figure 2. Typical entry screen for a new complaint record.

Example: FTA Applied to a Complaint Handling Process

Non-compliant complaint handling is frequently cited by the FDA in Warning Letters[6] to pharmaceutical and medical device manufacturers. Particularly for medical device manufacturers, the letters also frequently cite a failure to report in a timely fashion injuries or potential injuries resulting from the malfunction or misuse of a medical device, (in the form of Medical Device Reports (MDRs)). The complaint handling process is clearly a business process, which typically involves use of software for registering and processing the complaints. Commercial (Off-the-Shelf (OTS)) software exists to support complaint handling, such that a hypothetical case study can be presented and suggested as reference.

Figure 2 provides a typical view of an entry screen that might be employed for complaint handling. Almost all of these

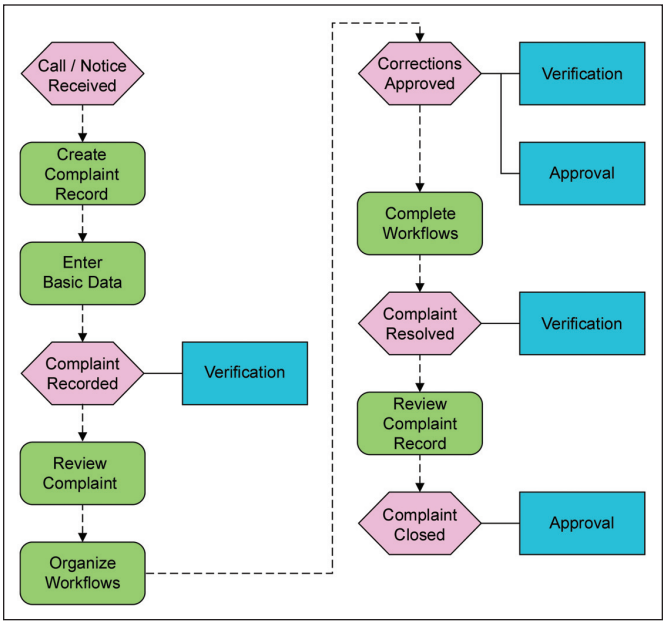

Figure 3. Complaint handling process.

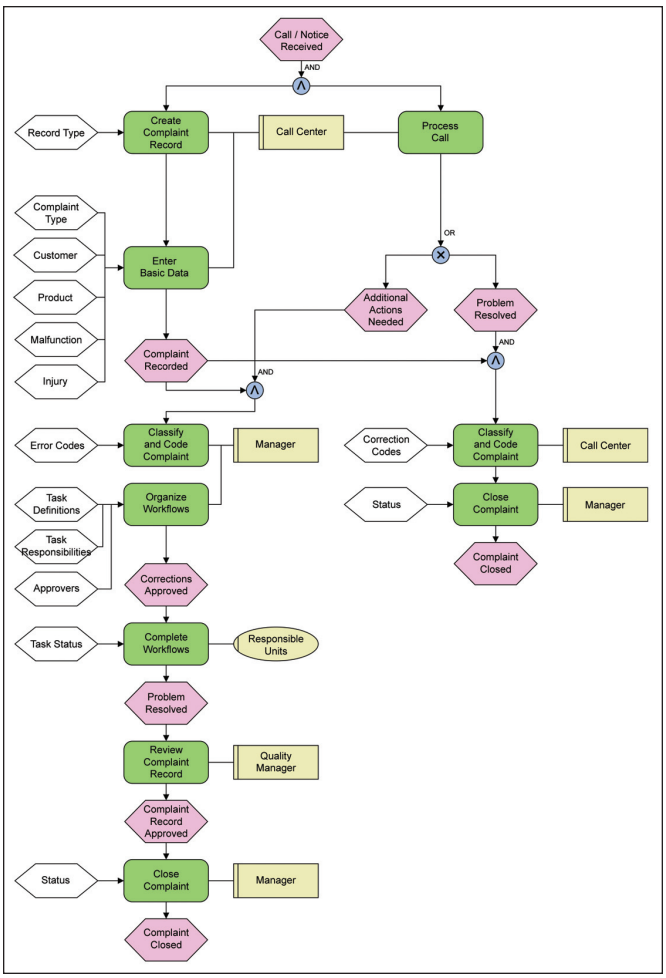

Figure 4. Complaint handling workflow.

fields are optional for creation of a complaint record, resulting in a very large user event space. It is clear that the standard configuration must be configured to limit user error. Clearly, user roles which limit access must be considered.

A precondition for applying FTA as a top-down risk assessment is an initial definition of the business process and software solution. Business processes are defined in this article by means of object-oriented process models, as is typically done in BPM.[7] A minimal definition of the system requires knowledge of system goals and the process workflow, including user roles and user inputs. Figure 3 provides a basic workflow process model of complaint handling, from the point of receiving the call and ending with the closure of the complaint. Figure 4 provides a more detailed model of the process chain, which includes actors and user inputs for individual process steps.

Taken from a balanced scorecard[8] or other information, a brief list of project goals for a complaint handling process for a medical device manufacturer commonly includes:

- support of filing MDRs in a timely manner, as needed
- customer assistance with use of device (help desk)
- registration of product defects and/or malfunctions from the field
- registration of patient injuries or potential injuries
- support of filing internal Corrective and Preventive Actions (CAPAs)

If top events (potential impacts) of the system are not known or there is inexperience in recognizing them, they can be perceived by taking a goal (quality objective), and formulating a negative hypothesis. Another approach is to identify the compliance-relevant electronic records, which are processed by the system. Top events should include major errors in that processing, e.g., loss of integrity.

An example of FTA is provided in Figure 5, starting with the top event, "MDR not filed on time." Possible user input errors which can lead to the top event are listed with the relevant data element. Combinations of errors which lead to the top event are joined with the logical functions OR or AND. The identified data elements can be considered to belong to the key process parameters for the process.

The FTA diagram does not include possible software defects, which also can lead to the top event. The added complexity to the diagram would probably inhibit a useful review by the user group, and it should be clear that user errors can be considered separately from software defects. It is anticipated that such top-level analyses would be primarily reviewed by the process owners and users, who are not expected to have much knowledge of the software solution during the early phases of the project.

From an initial inspection of the model, the following characteristics of the process can be inferred:

- Multiple pathways can lead to this failure, (i.e., the model has breadth).
- Simple combinations of user errors can lead to failure, (i.e., the model has little depth).
- At least two user errors can directly cause the failure (i.e., there is a significant probability of failure).

Keeping in mind that call centers are often outsourced, and thereby not always closely managed, a mitigation strategy based solely upon user training and limited user access will not usually result in a highly reliable process. The two errors which can directly result in failure originate from the person taking the call: to open a complaint record; and to select from the system the correct record type. Mitigation strategies involving software enhancements that could eliminate or inhibit some of the branches are certainly conceivable by the reader and should be available as options during the early project phases.

The relevant process parameters for the user errors modeled in Figure 5 should be included in the list of key process parameters for the system. Design review should focus upon user entry of these parameters and consider:

- user access to the entry field
- selection option list
- possible plausibility checks

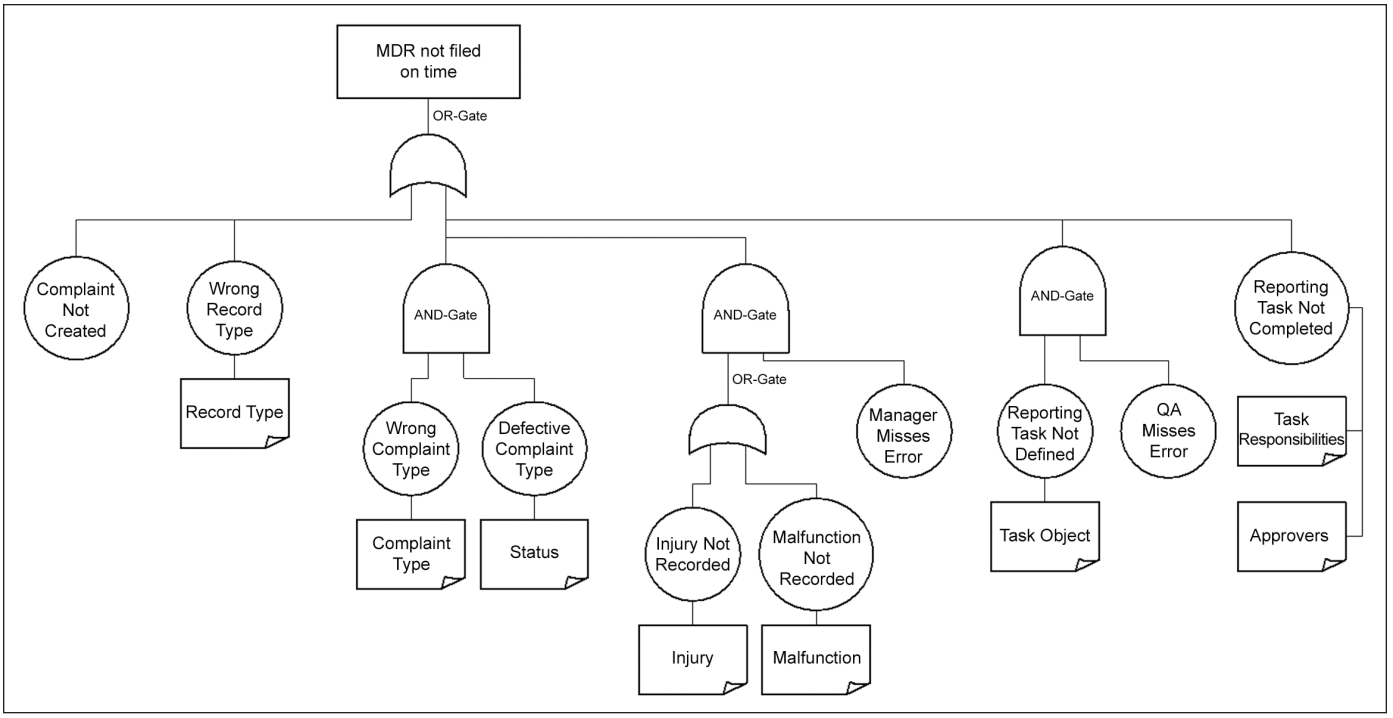

Figure 5. Fault Tree Analysis of user errors for top event, "MDR not filed on time."

To complete the top-down analysis, other failure scenarios would need to be analyzed similarly, starting from the project goals. For example, separate analyses also could be started from the top events "MDR is incorrect" and "Customer not helped." The number of such analyses can be limited by the number of goals set for the project and basically document the concerns addressed in the top-down analysis.

Although FTA is best for early analysis of combinations of errors, Figure 6 illustrates how critical software functions could be separately identified for the top event "MDR is incorrect." No detailed analysis of software is advisable at this level of detail, but FTA does directly associate basic functions with a top event and implicitly gives them a high ranking. Combinations of defects leading to this failure are not explored in this diagram. Such combinations would be expected to have a lower probability and thereby a lower ranking. Such an analysis could provide an orientation for detailed functional risk analyses later in the project.

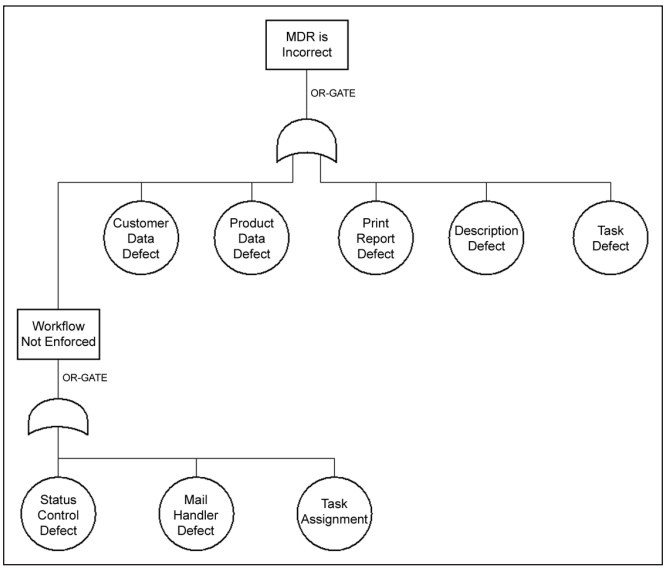

Figure 6. FTA of SW defects for top event "MDR is incorrect."

Upon completion, the design project has identified at an early stage the major risks of the system and cataloged the user errors which contribute to those risks. This catalog along with the failure scenarios would provide an excellent start for preparing training documentation and for subsequent functional risk analyses if used to identify critical software modules.

Conclusion

A top-level analysis should be conducted at the beginning of a project and helps to orient that project to address the major risks. It can be referenced for risk-based decision-making, and thus can guide early efforts for mitigating those risks. Preliminary employment of bottom-up analysis usually misses the "big picture" because dependencies and multiple failures are not easily included.

FTA is not a substitute for FMEA, in that it is not as useful for ranking and managing risks. When FTA is used early to identify critical modules, they can be transferred into FMEA for more detailed analysis. FTA is advisable for critical processes which are heavily dependent upon user input. It can be used to identify critical data and improve the design of user entry screens.

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Determining Minimum Number of Weigh Rooms to Meet Target Throughput

by Niranjan Kulkarni

This article presents a novel way for determining the number of weigh-dispense rooms required to meet the target throughput by employing Formal Concept Analysis (FCA) and Discrete Event Simulation (DES) techniques.

Introduction

As part of tablet manufacturing, the weigh-dispense process is the first process wherein the required raw materials are weighed and transferred to clean containers to be processed further. These weigh-dispense rooms, also referred to as central weigh, pharmacy, dispensary, dispensing, fractionation, and subdivision, are common to pharmaceutical manufacturing plants.[1] Studies exist detailing design and safety requirements for weigh-dispense rooms. From an operations perspective, layouts, error reductions during weighing, moving from manual to automated operations, etc., have been considered.

However, the issue of determining the number of weigh-dispense rooms required to meet target throughput has not been addressed. It is very important to address this issue, especially from an operations perspective when designing new facilities or renovating existing ones, as inadequate weigh dispensing can starve downstream processes and reduce the overall facility throughput. This article provides a methodology that can be adapted to decide on the weigh-dispense room requirements to meet a target throughput.

The proposed approach is a two-step process, and makes use of Formal Concept Analysis (FCA) and Discrete Event Simulation (DES) techniques. One of the major reasons for using FCA as a grouping technique is its unique ability to create clusters based on attribute sharing rather than attribute distance, which is a commonly used method in other clustering approaches. DES are then performed to determine the sufficiency of the preliminary number of weigh-dispense rooms to meet the target throughput. It should be noted that although the proposed methodology is used to determine weigh-dispense room requirements, this method is applicable for any problem involving grouping of attributes and throughput analysis.

Overview of Formal Concept Analysis

In order to increase the grouping efficiency, it is important to understand the underlying relation between objects and their attributes. This relationship, known as the incidence relationship, is represented in a tabular format and is binary in nature. The products can be thought of as objects and the relevant raw material they use as attributes. "X" in a cell indicates that an object has that particular attribute, i.e., a product requires a particular raw material as seen in Table A. The example in Table A indicates that Product 1 requires Raw Materials 1, 2, and 5.

This object-attribute relationship can be modeled using the concept analysis technique. According to the traditional logic ap-

Table A. Product – raw material incidence relationship.

Objects → / Attributes ↓	Product 1	Product 2	Product 3
Raw Material 1	X		X
Raw Material 2	X	X	
Raw Material 3		X	
Raw Material 4			X
Raw Material 5	X	X	X
Raw Material 6			X

proach, a concept includes an extent (objects covered by a concept) and intent (attributes covered by a concept). Furthermore, concepts can be arranged according to their hierarchical relation in form of a structured lattice.

In order to extract these concepts from the original relational dataset, Formal Concept Analysis (FCA) is employed. Classical FCA focuses on binary relations of the objects and their attributes representing them in the form of a concept lattice. The nodes of the lattice are essentially contexts, clusters of object(s), and attribute(s). The lattice, thus formed, displays all the interesting clusters (groups) in the data arranged in a hierarchical ordering. This feature distinguishes FCA from other methods for finding groups in data (clustering methods) which are, by and large, based on attribute distance rather than attribute sharing.[2] FCA is also a popular tool used for finding patterns and dependencies within data tables. These patterns in the data are referred to as formal concepts.[3] The mathematics behind extracting formal concept is out of scope of this article. It is sufficient to say that a formal concept is a maximal rectangle in the table. Interested readers are encouraged to check the article by Ganter and Wille[4] for mathematical and computational foundations of FCA.

Discrete Event Simulations

A model is a representation of a system or process. A discrete event simulation model is a computer representation of a system or a process that incorporates time and the changes that occur over discrete time intervals. The ability to model and evaluate stochastic events, perform "what-if" analyses, comparisons, and analyses are the key reasons for using computer simulation. Prediction of system performance, identification of system problems and their causes are the key results.[5] Furthermore, it is much more cost effective and significantly less risky to make changes to a computer model and analyze the performance of the system; as opposed to making changes to the real world system.

Large degree of variability often exists in processes, and the weigh-dispense process is not an exception. Variability in the process may arise due to operator dependency, technology, raw material quantity to be weighed, safety procedures to be followed while weighing certain raw materials, and cleaning between weighments, to name a few. Variability influences cycle times of the process, which in turn impacts throughput, subsequently influencing the required number of weigh rooms. Discrete event simulation has proven to be a particular useful decision making tool when dealing with variability inherent to the process.

There is a growing interest in using discrete event simulations within the pharmaceutical domain to analyze different problems including advertisements, promotions and pricing,[6] inventory,[7] supply chains, understanding material consumption over time, designing staging spaces, etc. Several commercially available discrete event simulation software programs are available.

Proposed Methodology

The methodology begins by developing the incidence relationship between objects (product) and attributes (raw material). This relationship is a binary relationship and indicates which raw materials are required to make a given product. Using the concept-forming operators (not covered in this article), all the concepts will be extracted. The most general formal concepts will represent the number of weigh-dispense rooms required.

These general concepts can be further grouped based on certain constraints such as product/raw material segregation, layout constraints, requirements for specific equipment, etc., using domain (product) knowledge. Subject Matter Experts (SMEs) can be consulted for this purpose. This step is referred to as "Human Intervention/Intelligence." Thus, the output obtained will provide the initial number of weigh rooms. To check whether the number of weigh rooms are adequate to realize the throughput targets, discrete event simulations can be performed.

The model designed for this purpose should represent the real-world scenario as closely as possible. Appropriate parameters, such as processing or setup times (and their associated variability), lead times, planned and unplanned downtimes, schedule and release patterns, operator/equipment requirements, etc., should be collected and modeled accordingly. Running simulations for the desired length of time will help to evaluate the adequacy of weigh-dispense rooms.

In the event that simulations indicate the number of rooms is adequate, there is a possibility that rooms could be combined in an attempt to reduce the room requirements. This can be done by "moving down" the hierarchical lattice structure to a more general and lower tier concept. On the other hand, simulations may reveal that weigh-dispense process is the bottleneck and that throughput cannot be realized with the current number of rooms. In such instances, it is recommended to first look into improving process and operational efficiencies (improvement opportunities should be explored even when simulations show that initial estimate of rooms are adequate. This may help reduce the room requirements. One may argue that we should have an improved process to begin with, which is perfectly acceptable, and has no change on the proposed methodology). Any improvement which reduces process times and/or variability has a positive impact on throughput. Implementing such changes are often less expensive than increasing the facility square footage. In some cases, adding operators (if that is the bottleneck), increasing number of hours/shift, or increasing number of shifts/day, etc., can prove to be more cost effective than adding another room. However, if the aforementioned options fail to meet throughput targets, it becomes essential to increase the number of weigh-dispense rooms. Under these situations, it is recommended that the bottleneck room(s) be selected for further analysis.

The number of rooms can be increased by two means, namely, increasing the room capacity or further sub-

dividing the products that are weighed in that room. This is referred to as the "split/increase" decision. Increasing capacity refers to the addition of another (similar) room, while splitting refers to the selection of specific concepts in the lattice. Increasing the number of rooms is an iterative procedure and will end once the number of weigh-dispense rooms satisfies the throughput requirements. The proposed methodology is shown in Figure 1.

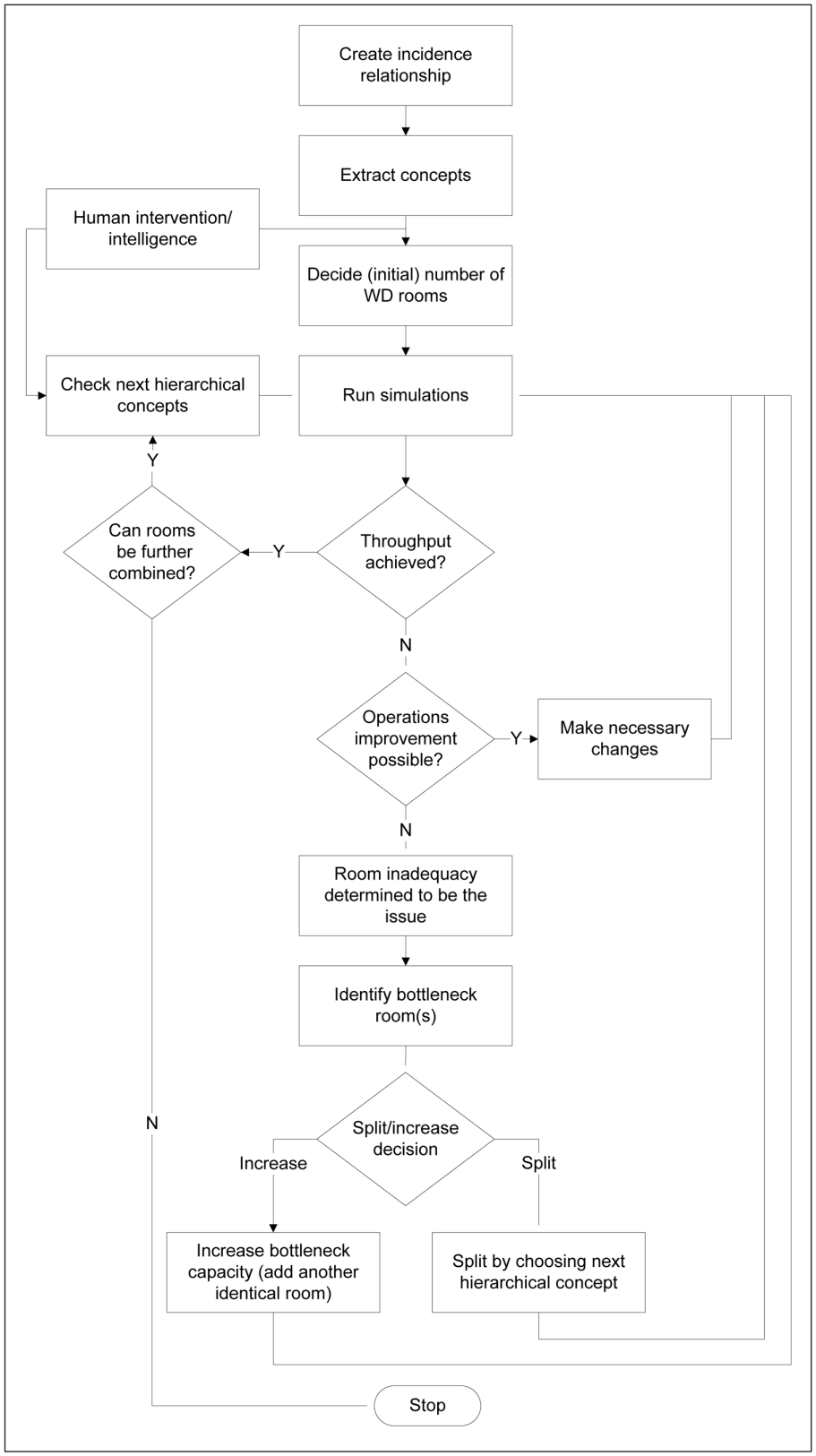

Figure 1. Proposed methodology.

Case Study

In a real life application, this methodology was applied to determine the number of weigh rooms required to meet the target throughput at an OSD facility. As per the proposed methodology, it is required to develop the incidence relationship between products and raw materials. The study comprised 24 product types, consuming almost 50 different raw materials (in different quantities). The incidence relationship is shown in Figure 2. The products are represented by upper case P (P1 – P24) and raw materials (A) are given in the first column (A1 – A48).

Formal concepts were extracted as the next step. The hierarchical concept lattice shown in Figure 3 is discussed in this article; the procedure to derive concepts and draw the lattice is not part of this article. The lattice nodes are contexts – product(s) and raw material(s). Higher up a product is placed in the lattice, greater is the requirement for raw materials; compared to a product placed at a lower hierarchy in the same cluster, e.g., P24 requires more raw material than product P1. The node at the top of the lattice (blue colored) indicates that none of the products use all the raw materials, and the node at the bottom of the lattice indicates the same thing from the raw material perspective. Essentially, these two nodes can be represented as $\{P, \Phi\}$ and $\{\Phi, A\}$ respectively. The concept lattice helps the user visually represent/understand clusters obtained, raw materials which are unique to certain products, and raw materials shared across other product clusters.

Several raw materials are shared across different product clusters, as seen in the lattice, e.g., raw materials A24 is required to make products P10 and P12. A4 is another such raw material that is required for products P10, P12 (along with A24), and is also required for products P1, P13, P17, P19, P23, and P24. Consequently, the concept involving A4 is considered a more "general" concept and is placed hierarchically below A24.

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P16	P17	P18	P19	P20	P21	P22	P23	P24
A1	x									x			x			x		x				x	x
A2	x									x			x			x		x				x	x
A3	x									x			x			x		x				x	x
A4	x									x		x	x			x		x				x	x
A5	x		x			x	x		x	x			x	x	x	x	x	x				x	x
A6		x		x	x																		
A7		x		x	x																		
A8		x		x																			
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A13						x	x		x						x		x						
A14							x										x						
A15						x	x		x						x		x						
A16						x	x		x						x		x						
A17							x										x						
A18						x	x		x						x		x						
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A48																							x

Figure 2. Incidence relationship – products and raw materials.

In instances when raw materials are shared by two or more products, SMEs have to decide the product clustering that makes the most sense. For example, Product P12 could have been grouped in the same cluster with P10, as both products require raw material A24, but P3, P14, and P12 share the same granulation equipment. So, despite using different raw materials, these products were clustered into a common weigh room without causing unnecessary delays between campaigns.

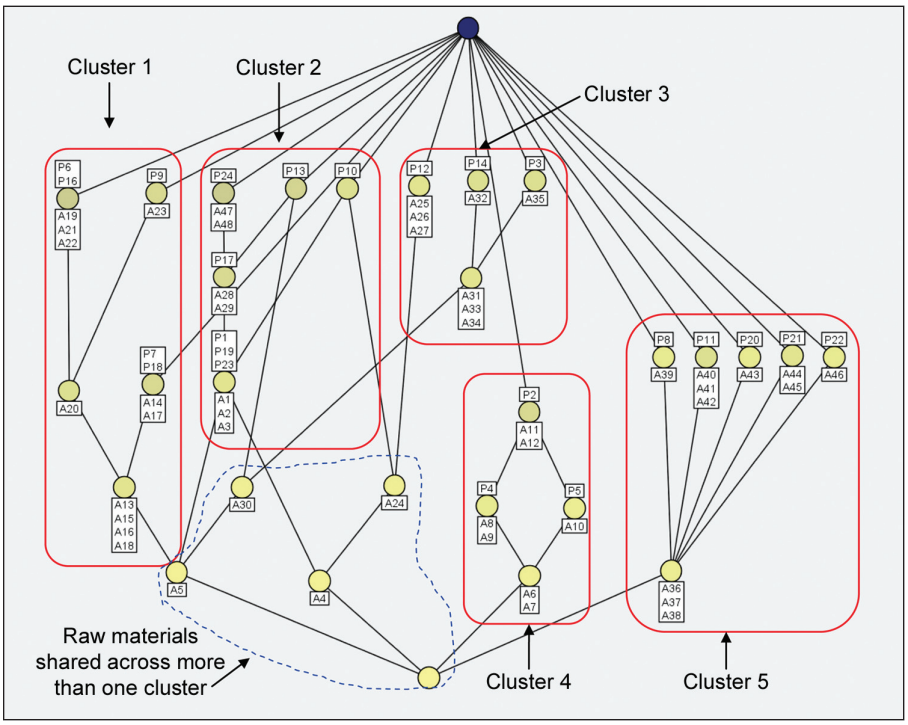

Figure 3. Hierarchical lattice structure.

Thus, using FCA and human intelligence/intervention, five product clusters are formed – highlighted in Figure 3. Each cluster represents a set of products with their required set of raw materials. This is the first estimate for (initial) number of weigh rooms. According to this estimate, five weigh rooms are required:

- Weigh-Dispense Room # 1 – Products 1, 10, 13, 17, 19, 23, 24
- Weigh-Dispense Room # 2 – Products 3, 12, 14
- Weigh-Dispense Room # 3 – Products 8, 11, 20, 21, 22
- Weigh-Dispense Room # 4 – Products 2, 4, 5
- Weigh-Dispense Room # 5 – Products 6, 7, 9, 16, 18

The rearranged incidence relationship table which show the aforementioned five weigh-dispense rooms and their product/raw material dedication is depicted in Figure 4. The shared raw material rows are repeated in this rearranged table, thus, the count of row will be more than 48 (initial number of raw material rows in the incidence relationship table).

Discrete event simulations were performed as the next step to check if this initial estimate for the number of rooms could meet the demand requirement. Detailed description of the modeling exercise is out of scope for this article; however, a brief overview of the key components of this study is provided:

- Data Collection
  - Product and personnel flow

observation – to understand the flow paths taken by each product group and required number of operators at every process step.

- Time/motion studies and data from SAP system – in case where time (cycle time; setup time; repair time; cleaning or changeover time; time required by forklift or operators to travel certain distance; etc.) is not recorded automatically, time and motion studies were performed. All other time stamps were retrieved from the SAP system.

- Line tours and observations.

- Data Fitting – collected data was fitted to appropriate statistical distributions in order to capture the stochastic nature of the processes.

- Model Building – FlexSim, a commercially available DES software was used for this purpose. A snapshot of the model is shown in Figure 5.

- Model Analysis – after determining the warm-up length (required to ensure steady state conditions are reached), and running the model for a predetermined run length, the essential performance indicator, especially the upstream throughput, was recorded.

The simulation results revealed that the throughput target was not achieved with just five weigh-dispense rooms. Significant delays and queue buildup was observed in front of weigh-dispense room 1 (bottleneck). Simulating for scenarios with reduced cycle times, reduced variability, increased operators, increased shift durations, etc., did not help meet the target throughput. Consequently, room inadequacy was determined to be the issue. The model showed that even though Products 1, 10, 13, 17, 19, 23, and 24 share many of the same ingredients, two separate rooms would be required. It was decided to increase the capacity of room 1 by adding a second room. The products

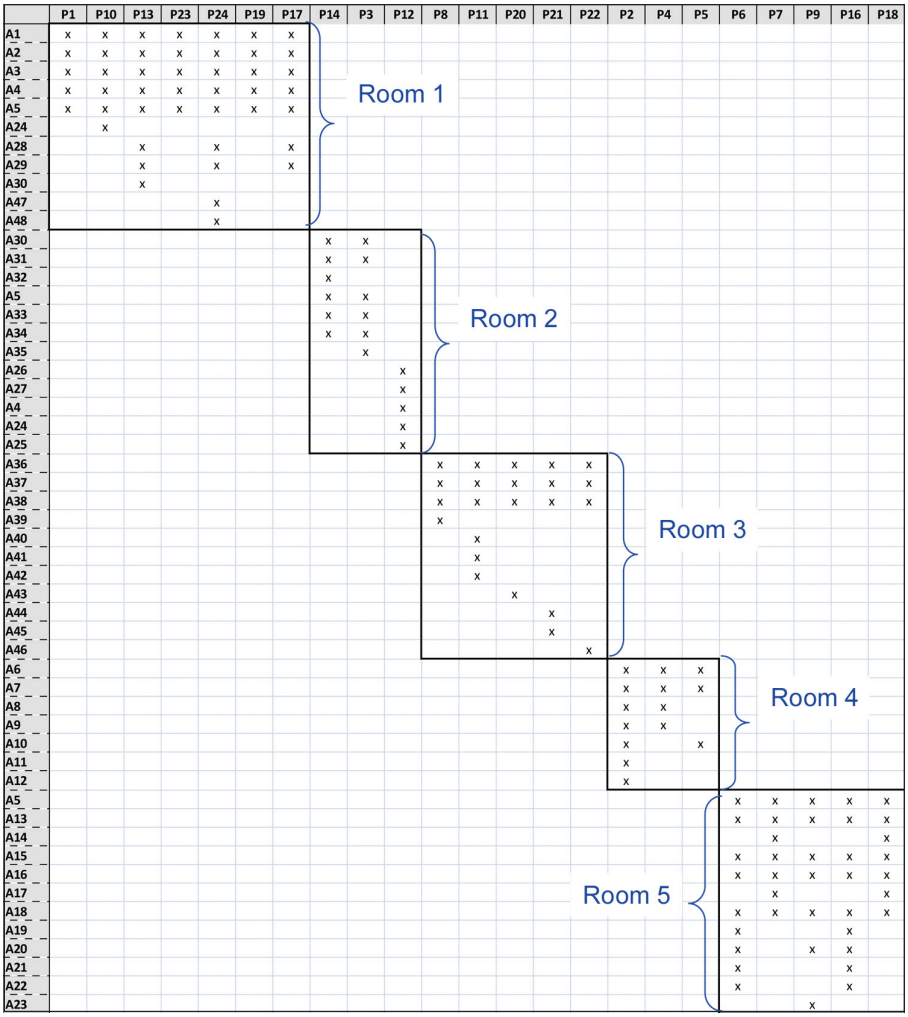

Figure 4. Weigh rooms required per formal concept analysis and human intelligence.

requiring more raw material – P13, P17, and P24 would be weighed and dispensed in one room, while the remaining products from the original product cluster would be weighed and dispensed in the other room.

Based on this analysis, it was concluded that six (dedicated) weigh

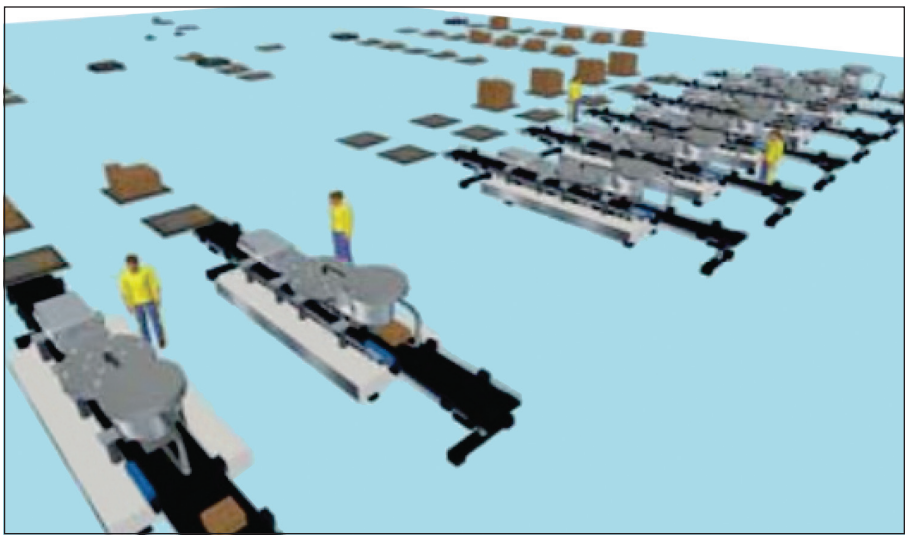

Figure 5. Snapshot of the simulation model.

"Though the proposed methodology is applied to determine the number of weigh rooms required in an OSD facility, this method is equally applicable in cases that require product grouping and capacity analysis."

rooms should be used. The final product clusters (rooms) are shown in Figure 6. These six dedicated weigh rooms were:

- Weigh-Dispense Room # 1 – Products 1, 10, 19, 23
- Weigh-Dispense Room # 2 – Products 13, 17, 24
- Weigh-Dispense Room # 3 – Products 3, 12, 14
- Weigh-Dispense Room # 4 – Products 8, 11, 20, 21, 22
- Weigh-Dispense Room # 5 – Products 2, 4, 5
- Weigh-Dispense Room # 6 – Products 6, 7, 9, 16, 18

Conclusions and Discussions

In this article, a novel methodology for creating room clusters and confirming their sufficiency to meet a target throughput is presented. Clusters are formed using Formal Concept Analysis – a technique popular in data mining and pattern recognition communities. FCA forms clusters based on the object-attribute relationship, as opposed to the distance. For smaller datasets, the concepts can be extracted without using any software.

It should be noted that the FCA technique clusters only according to the binary relationship between the objects and their attributes. So other constraints, namely, raw material quantities consumed by a product, technology constraints, etc., are not considered. Such considerations should be included by SMEs while determining the initial number of clusters (rooms).

Once the initial number of rooms is obtained, discrete event simulations are used to determine adequacy. The major indicator of adequacy is the ability to meet the target throughput within given time frame. If these targets are not met, the capacity of the bottleneck room(s) should be increased or it may be required to split the product cluster, i.e., choose the next hierarchical concept.

Though the proposed methodology is applied to determine the number of weigh rooms required in an OSD facility, this method is equally applicable in cases that require product grouping and capacity analysis. Such analysis should be undertaken when designing new facilities or renovating existing facilities and designing new or evaluating existing processes. Furthermore, this method can be employed not only in case of designing new facilities, it also can be applied to an existing facility to account for future product additions. In the later case, new product(s) and raw materials will be added to the incidence relationship table and the process described in Figure 1 will be repeated. Additionally, the methodology can be applied to several other areas, such as quality, supply chain, maintenance, etc.

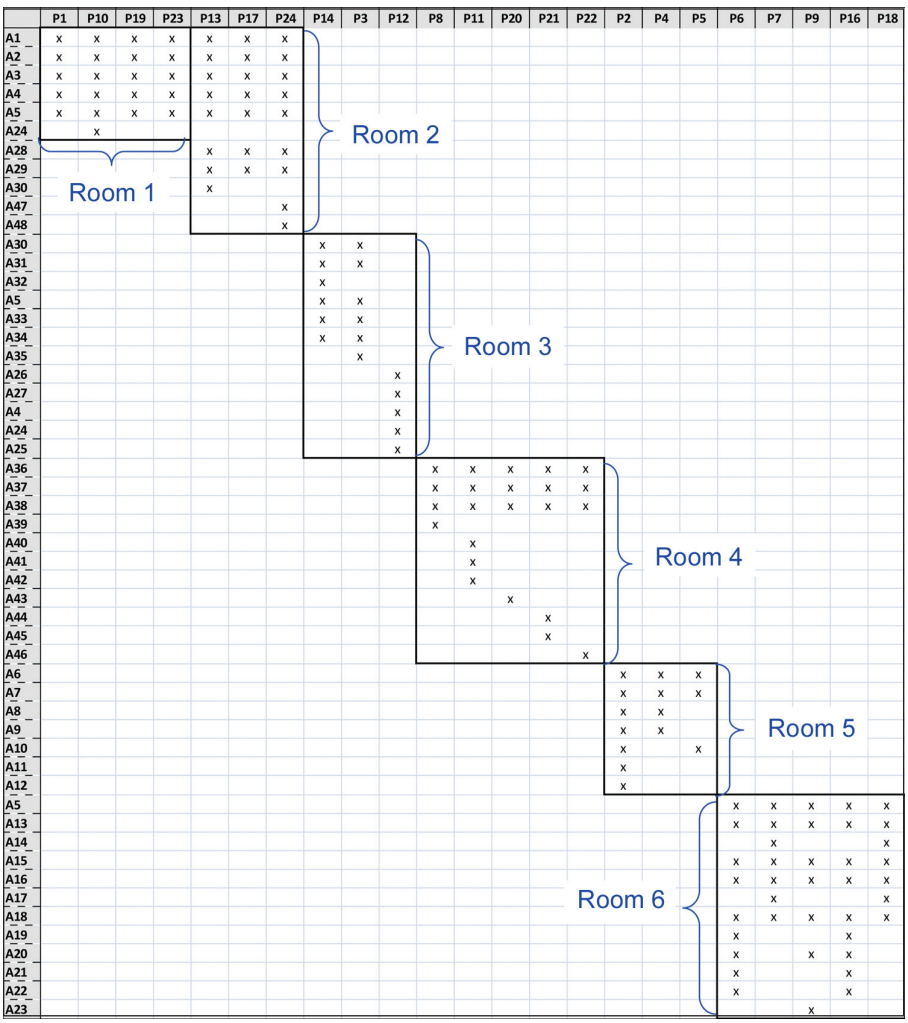

Figure 6. Weigh rooms required per discrete event simulation modeling.

Keywords

- Formal Concept Analysis (FCA)

- Discrete Event Simulation (DES)
- Product Grouping
- Weigh-Dispense Rooms

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Japan Affiliate Visiting Mission Returns to North American Plants

by Osamu Matsumoto and Michael Lucey

As one of the highlights of the Affiliate's yearly program, the 2011 tour of overseas pharmaceutical plants began in late October in Ontario, Canada, and was concluded one very full week later on the East Coast of the US. All tour registrants then transferred to Dallas, Texas, to participate in the ISPE Annual Meeting.

In the several months of set-up, the Plant Tour Organizing Committee met on a regular basis at the Affiliate offices in Yushima, Tokyo. Adjunct Directors Mason Waterbury and Michael Lucey were responsible for closely coordinating with Canada and the US, while the "in-Japan" arrangements fell within the scope of Affiliate Officer Shigeru Nakamura and Directors Osamu Matsumoto and Masayuki Akutagawa.

The group that travelled was made up of three of the organizers and sixteen delegates from Japan's pharmaceutical industry. The total party was well balanced: five from pharmaceutical companies, seven from engineering companies, four from construction companies, and three from equipment fabricators.

For this first ever Affiliate plant tour to Toronto, the Canada Chapter warmly welcomed the Japanese mission and carefully managed the visiting schedule throughout. Conveniently located for visiting in the city suburbs were Therapure, a contract manufacturer for bio-products production, and Patheon, a contract manufacturer for solid dosage production, both of whom extended a warm hand of friendship to the Affiliate. Easily accessed too was Sanofi Pasteur, the famed large-scale vaccine manufacturer, who proved to be a fine host. The Chapter-Affiliate reception in the final evening in Ontario was a time for exchanging views over ice wine in a historic downtown setting.

Highly impressive was AstraZeneca's research laboratory in Boston where, following a detailed presentation on many aspects of the laboratory, the tour members were guided in two parties through the glass-walled open-plan R&D facility, with its highly functional use of space and focus on "communication" and "innovation."

Mission members and hosts in front of AstraZeneca R&D Boston, Massachusetts, after the facility tour.

Presentation by MedImmune to the mission members at their facility in Frederick, Maryland.

The Affiliate was delighted to be offered the opportunity by 2011 Facility of the Year Category Award (FOYA) Winners Merck and MedImmune to walk down their facilities. Merck adopted modular construction to revamp its existing solid dosage plant in a short period and at a competitive construction cost. The subsequent visit to MedImmune permitted thorough explanations to be received and a tour of the company's monoclonal antibody production plant. Tour members admired the "dedicated training lab" for employees and efficient production management. The following week at the Annual Meeting in Dallas, it was learned that MedImmune had been crowned as Overall 2011 FOYA Winner. Returning to downtown Washington D.C., presentations and opinion were exchanged over dinner with a noted former US FDA regulator, at an event hosted by the Japan Affiliate.

To complement the "work" aspects of the tour, sightseeing breaks included Niagara Falls and New York City, as well as Washington D.C., as a time for relaxation for tour participants from the demanding daily "dose" of English language requirements built into a rigorous travel and visiting schedule. Further standout moments in the sightseeing schedule were the viewing of the grave of President Kennedy, and the memorial museum in Dallas.

In planning the plant tour, the highest possible level of cooperation was received from the host plants and organizations visited, as well as from ISPE staff in the US and Japan. The Affiliate would like to take this opportunity to express its deep gratitude to all for the opportunity to rewardingly end a challenging year in the wake of the 11 March earthquake and tsunami. Now, at the rescheduled 10th anniversary Meeting in Hiroshima on 12 and 13 April, the Affiliate is warmly welcoming all friends, new and old.

Perhaps in the spirit of a part of the tour, a paraphrasing of the late President Kennedy is called for: "Don't ask what ISPE can do for you. Ask what you can do for ISPE."

ISPE's Operations Management Community to Develop New Guide: Seeks Input and Volunteers

The traditional driving forces dominating the pharmaceutical industry are changing:

- The rate of innovation is expected to decrease significantly while R&D costs are anticipated to increase.
- High expectations for growth continue, regardless of the severity of the challenges faced by the industry.
- Heterogeneity of customer preferences is increasing.
- Pressure on prices due to governmental budget shrinking is steadily increasing.

Therefore, the logical question to ask is whether operational efficiency truly makes a difference in contributing to the bottom line. When we consider that the three most effective means for increasing financial performance are through more efficient marketing, R&D, and operations, but studies indicate costs associated with Marketing and R&D will not be declining in the near future, the logical conclusion is to assume that focusing on Operational Excellence will directly affect business performance in a positive manner.

In support of its mission to review all areas of operations management, which includes the integrated process flow from the supply of raw materials to final product distribution, ISPE's Operations Management Community of Practice is engaged in producing the first ISPE guidance document, tentatively titled the Pharmaceutical Operations Management Guide, which will focus entirely on operations management.

The primary objectives of the Pharmaceutical Operations Management Guide are to:

- Provide guidance and support to pharmaceutical operations managers to be able to select the most appropriate solutions for the identification and completion of the objectives of their manufacturing operations within the framework of the entire organization. This includes stake holders and regulatory bodies.
- Provide operations management personnel with sound support in understanding how compliance and operational excellence can be achieved through a mutually beneficial approach between industry and regulatory, considering the extent of such tight regulation that currently exists in the pharmaceutical industry.
- Define a common language and provide a guideline for performance measurement and improvement.
- Identify new performance improvement tools, while clarifying what is and is not applicable in pharmaceutical operations.
- Provide a reference or benchmark for pharmaceutical operations.

The scope of the document will range from global operations strategy to plant shop-floor execution and it will specifically address operations strategies, supply chain management, performance measurement, and performance improvement tools.

The new guide will contain five comprehensive chapters that support the above-mentioned objectives including:

1. **Introduction**
   - A. Background and an overview of recent changes in the industry
   - B. A medicine is not a specific product
   - C. Mission of industrial operations functions
   - D. Organization of manufacturing operations
   - E. Key Performance Indicators (KPI)
   - F. Purpose of the guidance
2. **Supply Chain Strategy and Management** – designed to provide industry professionals with an insight on aspects to be considered when designing and implementing a supply chain emphasizing the importance of seamless integration.
3. **Manufacturing Operations Strategy and Management** – with the understanding that ultimately Manufacturing Operations Strategy aims to maximize capital/resources effectiveness in order to support the achievement of business objectives and deliver additional value to the supply chain, this chapter will detail the link between manufacturing operations strategy with the company competitive strategy, manufacturing technologies, and assets planning and management.
4. **Key Performance Indicators** – demonstrate the importance of establishing a well-structured set of KPIs that enable results measurement to support supply chain improvement and manufacturing operations effectiveness.
5. **Continuous Improvement and Innovation** – provide strategies for performance improvement; major improvement methods and tools; innovation management; and a long-term plan that includes the mission, vision, accelerators and threats, SWOT analysis, and other pertinent data.

The guide will attempt to answer questions that all professionals in the pharmaceutical industry are struggling with, regardless of whether they are working for the originator or generics. For that reason the Operations Management COP Steering Committee is seeking input and participation from volunteers willing to share their thoughts and ideas about how this new guide can effectively aid industry professionals in better understanding how pharmaceutical industrial operations can be operated and managed more efficiently to increase productivity and value for all shareholders.

Questions to be addressed regarding this guide include:

1. Is there a demonstrated need to provide guidance to operations management personnel as detailed by the primary objectives of the guide?

Concludes on page 3.

...Operations Management Guide

Continued from page 2.

2. Is the scope of the document appropriate?
3. Are there any other topic areas that should be added to or deleted from the scope?
4. What general thoughts and ideas do you have regarding what should be addressed in this guide?
5. Would you buy and/or recommend a guide based on this material?

Please respond to these simple questions by accessing a survey: http://operationsmanagementcopsurvey.questionpro.com/. You may also contact ISPE Volunteer Services at volunteerservices@ispe.org for additional information.

Volunteers who are subject matter experts with demonstrated expertise in developing manufacturing indicators; researching or benchmarking experience in KPI definition; manufacturing data collection systems and analysis (MES, OEE, etc.); generally knowledgeable about multifaceted dimensions of industrial operations; and previous experience or involvement in developing ISPE guidance are invited to join the Good Practice Guide Task Team. Please contact ISPE Volunteer Services at: volunteerservices@ispe.org and a member of the task team will follow up with you.

ISPE to Develop Guidance Documents on the Facility of the Future

ISPE's Active Pharmaceutical Ingredients (API) community envisions a future of integrated API and drug product manufacture and plans to develop ISPE Guidance Documents discussing this vision.

"A single-factory manufacture of Drug Product (DP) starting from excipients and API intermediates," writes the API Community of Practice (COP) in the Pharmaceutical Engineering Jan/Feb 2012 Online Exclusive article, "Facility of the Future." This would be an integrated facility with real time release of API into DP, minimum or zero API storage, and very fast supply chain response. Processes would be developed by a single development team enabling them to deal with linkages between API and DP without organizational barriers."

The *Pharmaceutical Engineering* article discusses the next generation of facilities, equipment, and processes as part of the "API Small Molecule Plant of the Future." The concepts will form the basis of a series of planned ISPE Good Practice Guides. The API COP would like ISPE Members to provide feedback on this endeavor through a survey included in the article.

Timely ISPE Guide to Provide Best Practices for Comparator Management

As the spotlight on Comparative Effectiveness Research (CER) increases, ISPE is producing a Guide on Comparator Management. Scheduled for a March 2012 release, the Guide will provide the bio/pharma industry with a complete picture of the steps that need to be followed to execute a clinical study that includes comparators. It also gives advice on how to make the right purchasing decisions in selecting/acquiring comparators and avoid costly delays in comparator trials.

Comparative effectiveness research is designed to inform healthcare decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options, according to the US Agency for Healthcare Research and Quality. The evidence is generated from research studies that compare drugs, medical devices, tests, surgeries, or ways to deliver healthcare.

The global trend is that the importance of comparative effectiveness research is increasing. The most recent US legislation supporting CER is the healthcare reform law, which establishes the Patient-Centered Outcomes Research Institute (PCORI) as an independent advisory board with a $3 billion budget to set the CER national priorities and research agenda. The Comparative Effectiveness Resource Center of the nonprofit ECRI Institute provides complete lists of comparative effectiveness research legislation, stakeholders, and news reports.

The ISPE Good Practice Guide: Comparator Management is intended to establish strategic and tactical considerations when sourcing and procuring comparators for use in a clinical trial. It aims to identify and develop industry good practices for: making sourcing decisions, technical considerations for blinding, and release for use. One of the main benefits of the Guide is that it provides a unique overview of the management of a sponsor's comparator needs. Guide authors say this Guide is the first of its kind in the industry and can potentially save pharmaceutical companies and research teams significant time and money.

2012 Facility of the Year Awards (FOYA) Winners Announced

The Facility of the Year Awards Judging Panel has named five Category Award Winners and selected one project for Special Recognition in the 2012 Facility of the Year Awards (FOYA) program. The winning projects for 2012 are located in Germany, India, Ireland, Italy, and the USA. The winning companies and respective award categories are:

- **Chiesi Farmaceutici S.p.A.,** winner of the Facility of the Year Award for Sustainability for its Chiesi Farmaceutici Research and Development Centre facility in Parma, Italy
- **Eisai Pharmatechnology & Manufacturing Pvt. Ltd.,** winner of the Facility of the Year Award for Project Execution for its Eisai Knowledge Centre facility in Visakhapatnam, Andhra Pradesh India
- **Merck & Co., Inc.,** winner of the Facility of the Year Award for Facility Integration for its Merck Vaccine Bulk Manufacturing Facility (VBF) Program of Projects in Durham, North Carolina, USA
- **Rentschler Biotechnologie GmbH,** winner of the Facility of the Year Award for Equipment Innovation for its REX III manufacturing facility in Laupheim, Germany
- **Roche Diagnostics GmbH,** winner of the Facility of the Year Award for Operational Excellence for its TP Expand project in Penzberg, Germany
- **National Institute for Bioprocessing Research and Training (NIBRT),** winner of the Facility of the Year Award Special Recognition for Novel Collaboration for its New Greenfield facility in Dublin, Ireland

The FOYA program is the pharmaceutical industry's premier awards program dedicated to celebrating innovation and accomplishments in facility design, construction, and operation. The Facility of the Year Awards program recognizes state-of-the-art pharmaceutical manufacturing projects that utilize new and innovative technologies to enhance the delivery of a quality project, as well as reduce the cost of producing high-quality medicines. Now entering its ninth year, the awards program effectively spotlights the accomplishments, shared commitment, and dedication of individuals in companies worldwide to innovate and advance pharmaceutical manufacturing technology for the benefit of patients worldwide. The Facility of the Year Awards program is sponsored by ISPE, INTERPHEX, and Pharmaceutical Processing magazine.

"Our 2012 Category Winners reflect the true spirit of the Facility of the Year Awards program," said Judging Panel Chairperson Chaz Calitri. "The winning projects exemplify innovation in pharmaceutical manufacturing for the benefit of patients all over the world, who depend upon us for medications that are high quality, available and affordable. Our winners come from five different countries and include novel, low cost biologics facilities, creative and visionary industry-academia-government collaborations, and hyper-fast track investments made to ensure vaccine's get to patients in need. We are also proud this year to recognize facilities that seek to speed up drug development as well as facilities that greatly reduce the environmental 'footprint' of manufacturing in the communities in which they reside."

The Facility of the Year Awards program is truly global, as submissions over the past eight years have been received from more than 25 different countries and territories. Each of the submissions was reviewed by an independent, blue-ribbon judging panel consisting of global senior-level executives from all aspects of the industry. The judging panel met personally in December to select the Category Awards Winners and select the 2012 Overall Winner, which will be announced to the world for the first time at ISPE's Annual Meeting in November.

2012 Facility of the Year Events

There will be several opportunities to learn first-hand about the facilities being honored as "best in their class." These opportunities include:

INTERPHEX2012 – Attendees will be able to meet the Category Award Winners at the Facility of the Year Awards Display Area near the front of the exhibit hall of the Jacob K. Javits Convention Center in New York City, New York, USA. Team members from winning companies will be on-hand to discuss the success stories associated with these pharmaceutical manufacturing facilities. More information, including registration information, can be found at www.interphex.com.

ISPE 2012 Annual Meeting – Category Winners will give presentations about their winning projects during ISPE's 2012 Annual Meeting, 11-14 November in San Francisco, California USA. The highly anticipated announcement of the 2012 Facility of the Year Awards Overall Winner will also take place during the Keynote Session of this event. Information and updates on this global event can be found at www.ISPE.org.

Feature Articles – Comprehensive coverage will appear in *Pharmaceutical Processing* magazine and *Pharmaceutical Engineering* magazine.

Comprehensive details about each of this year's award-winning projects and their support teams, plus additional information on the awards program itself, can be found at www.FacilityoftheYear.org.

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EI Associates, 8 Ridgedale Ave., Cedar Knolls, NJ 07927. (973) 775-7777. See our ad in this issue.

NNE Pharmaplan, Vandtarnsvej 108-110, 2860 Søborg, Denmark. +45 44447777. See our ad in this issue.

Pharmadule Morimatsu AB, DanvikCenter 28, SE – 131 30 Nacka, Sweden. +46 (0)8 587 42 000. See our ad in this issue.

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IMA Life S.r.l., Via Petrarca, 34/40 50041 Calenzano (Firenze), Italy. +39 055 883231. See our ad in this issue.

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GEA Westfalia Separator, 100 Fairway Ct., Northvale, NJ 07647. (800) 722-6622. See our ad in this issue.

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AES Clean Technology, 422 Stump Rd., Montgomeryville, PA 18936. (888) 237-2532. See our ad in this issue.

Plascore, 615 N. Fairview, Zeeland, MI 49464. (800) 630-9257. See our ad in this issue.

Consulting

HYDE Engineering + Consulting, 6260 Lookout Rd., Suite 120, Boulder, CO 80301. (303) 530-4526. See our ad in this issue.

NNE Pharmaplan, Vandtarnsvej 108-110, 2860 Søborg, Denmark. +45 4444 7777. See our ad in this issue.

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Camfil Farr APC, 3505 S. Airport Dr., Jonesboro, AR 72401. (866) 530-5474. See our ad in this issue.

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Robert Bosch Packaging Technology, 8700 Wyoming Ave. N., Brooklyn Park, MN 55445. (763) 424-4700. See our ad in the issue.

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MKS Instruments, 2 Tech Drive, Suite 201, Andover, MA 01810. (800) 227-8766. See our ad in this issue.

Testo Inc., 40 White Lake Rd., Sparta, NJ 07871. (800) 227-0729. See our ad in this issue.

Measuring Instruments

Bürkert, Christian-Bürkert-Strasse 13-17, D-74653 Ingelfingen, Germany. +49 (0)7940 10-0

Endress + Hauser, 3 rue du Rhin, B.P. 150, 68331 Huningue Cedex, France. +0 825 888 001. See our ad in this issue.

Particle Measuring Systems, 5475 Airport Blvd., Boulder, CO 80301. (800) 238-1801. See our ad in the issue.

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Frewitt SA, Rte du Coteau 7, CH-1763 Granges-Paccot, Switzerland. +41 (0) 26 460 74 00. See our ad in this issue.

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Alfa Laval Inc., 5400 International Trade Dr., Richmond, VA 23231. (804) 222-5300. See our ad in this issue.

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GEA Mechanical Equipment, 90 Evergreen Dr., Portland, ME 04103. (207) 797-9500. See our ad in this issue.

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ProPharma Group, 10975 Benson Dr., Suite 330, Corporate Woods Bldg. 12, Overland Park, KS 66210. (888) 242-0559. See our ad in the issue.

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ELETTRACQUA Srl, Via Adamoli 513, 16141 Genova, Italy. +39 0108300014. See our ad in this issue.

Hanovia, 780 Buckingham Ave., Slough, SL1 4LA, United Kingdom. +44 (0) 1753 515300. See our ad in this issue.

MAR COR Purification, 4450 Township Line Rd., Skippack, PA 19474. (484) 991-0220. See our ad in this issue.

MECO, 12505 Reed Rd., Suite 100, Sugar Land, TX 77478. (800) 421-1798. See our ad in this issue.

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International

European Medicines Agency and US Food and Drug Administration to Share Manufacturing Site Inspections[1]

The European Medicines Agency and the US Food and Drug Administration (FDA) are launching an initiative to share work on inspections of manufacturing sites in each other's territories. The initiative, starting in January 2012, will enable the two authorities to rely on each other's inspection outcomes rather than carrying out separate inspections in duplicate. This is expected to:

- enable better use of the two authorities' inspection resources
- reduce the burden of inspections for medicines manufacturers
- shift the authorities' inspection capacity to other regions

USP Proposes Standard to Offer Best Practices to Help Ensure Supply Chain Integrity, Reduce Risks of Counterfeit or Mishandled Medicine[2]

As the pharmaceutical industry continues to globalize, the challenges of securing complex supply chains and protecting patients from counterfeit medicines, as well as the consequences of lapses in security or proper handling, have mounted. In an effort to encourage comprehensive public standards across the pharmaceutical industry, the U.S. Pharmacopeial (USP) Convention is proposing a set of recommended best practices that will help ensure that medicines can be traced back to their original manufacturer, are not adulterated or counterfeited, and are transported to their intended destination with their quality intact. USP is seeking broad feedback on these recommendations on supply chain integrity, which are posted at www.usp.org/USPNF/notices/generalChapter1083.html.

ICH

M3(R2) Q&As on Combination Drug Toxicity Testing Available on the ICH Website[3]

In December 2011, the ICH M3(R2) Implementation Working Group finalized under Step 4 of the ICH Process an additional set of questions and answers addressing combination drug toxicity testing. This new section was added to the three existing topics finalized in June 2011 and the Q&A document was renamed R1. The updated M3(R2) Q&A document is available for download from the M3 Section on the Multidisciplinary Guideline page at http://www.ich.org/products/guidelines/multidisciplinary/article/multidisciplinary-guidelines.html.

Asia/Pacific Rim

Australia

Australian TGA publishes *Reforms: a Blueprint for TGA's Future*[4]

The Australian Government has released its response to several major reviews of therapeutic goods regulation that have been undertaken over the past 18 months. These reviews include:

- the review to improve the transparency of the Therapeutic Goods Administration
- public consultations on the regulatory framework for advertising therapeutic goods
- the Auditor-General's report on Therapeutic Goods Regulation: Complementary Medicines
- an informal working group examining the regulation of complementary medicines and reasons for low compliance rates
- public consultations on the medical devices regulatory framework
- the Working Group on Promotion of Therapeutic Products
- the Health Technology Assessment Review

For more information, see http://www.tga.gov.au/newsroom/media-2011-tga-reforms-111208.htm.

Australian TGA Publishes Presentations on Manufacturing Therapeutic Goods[5]

Presentations on the following topics are now available on the TGA website: Validation and Qualification; GMP Audits; Clinical Trials; Release of Therapeutic Goods for Supply in Australia; and Quality Risk Management. For more information, see http://www.tga.gov.au/newsroom/events-presentations-manuf.htm.

China

SFDA Issues Document Standard for Administrative Law Enforcement on Health Food and Cosmetics Supervision (interim)[6]

In order to strengthen the supervision and management of health food and cosmetics, standardize the administrative law enforcement on health food and cosmetics supervision, the State Food and Drug Administration (SFDA) formulated the Document Standard for Administrative Law Enforcement on Health Food and Cosmetics Supervision (interim) in accordance with the Administrative Penalty Law, the Food Safety Law, the Regulations Concerning the Hygiene Supervision over Cosmetics and relevant laws and regulations. The Document Standard was issued recently and went into force as of 1 January 2012.

Chinese SFDA Commissioner Shao Mingli Meets Vice President of the Council of Ministers of Cuba[7]

On 26 December 2011, Shao Mingli, Commissioner of the State Food and Drug Administration (SFDA), met with the visiting Mr. Ricardo Cabrisas Ruiz, Vice President of the Council of Ministers of Cuba, and his entourage in Beijing. Both sides reviewed the long-time and effective cooperation in the medicine and health field between both governments and discussed relevant issues on biomedicine. Main directors of SFDA's Department of International Cooperation, Department of Drug Registration, and relevant directors of the Center for Drug Evaluation of SFDA attended the meeting.

Japan

Japanese PMDA Publishes "The Basic Concept on Regulatory Science in PMDA"[8]

The purpose of regulatory science researches in PMDA is to carry out fairly, precisely, and swiftly the three services, i.e., reviews of pharmaceuticals and medical devices, safety measures and

relief services for adverse drug reactions, and to contribute actively to the improvement of the public health and safety. The promotion of the research allows PMDA to provide more effective and safer pharmaceuticals/medical devices to the medical front in a quicker manner and to make more exact judgments of efficacy and safety from the scientific viewpoint. This is expected to promote international harmonization and enable the Agency to actively play the expected role in the international community. To promote regulatory science research, including Health Technology Assessment Measures against infectious diseases, PMDA will fulfill the expected role through cooperative research with related external institutions. Given the fact that regulatory science is the science of prediction, assessment, and harmonization based on data, regulatory science research in PMDA is considered to have an aspect which aims to show ideal direction and way of thinking based on certain facts, data, and results to develop various arguments and to integrate them into a certain direction.

Singapore

New Chairman Appointed to the Board of Singapore's Health Sciences Authority[9]

Professor John Wong Eu Li was appointed the Chairman of the Health Sciences Authority on 1 January 2012. Professor Wong, Isabel Chan Professor in Medical Sciences, is the Vice Provost (Academic Medicine) of the National University of Singapore. He is also the Deputy Chief Executive of the National University Health System, and Director of the National University Cancer Institute, Singapore.

Europe

Denmark

Danish Medicines Agency Creates New Medical Devices Website[10]

The Danish Medicines Agency's website, medicaldevices.dk, and the Danish version, medicinskudstyr.dk, have been redesigned and now welcomes users with a new and improved content structure, providing more accurate and relevant search results. The goal has been to develop an inviting and well-arranged website where users can find what they are looking for quickly. The design and content have been organized so that it ensures a high degree of recognizability with dkma.dk, which was launched in January 2011.

Danish Medicines Agency Creates Smart Phone App Allowing Consumers to Look up Medicines[11]

In Denmark, people can now check medicines via a new free app for mobile phones. The app is called "Medicintjek", which literally means medicine check, and it's available for download on iPhone and Android mobiles. It is a service offered free of charge by the Danish Medicines Agency for anyone interested.

European Union

European Medicines Agency Submits Concept Paper for Public Consultation: Delegated Act on the Principles and Guidelines of Good Manufacturing Practice for Active Substances in Medical Products for Human Use[12]

On 1 July 2011, Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use in regard to prevention of the entry into the legal supply chain of falsified medicinal products was published. This Directive amends Directive 2001/83/EC on the Community code relating to medicinal products for human use. Directive 2011/62/EU places an obligation on Member States to take appropriate measures to ensure that manufacturers of active substances on their territory comply with Good Manufacturing Practice (GMP) for active substances. It also places an obligation on the Commission to adopt, by means of delegated acts, the principles and guidelines of good manufacturing practice for active substances. This concept paper is being released for public consultation with a view to preparing the delegated act. The adoption of the delegated act is planned for 2013.

United Kingdom

Britain Launches New MHRA Website Homepage[13]

MHRA announced the launch of a new home page for the website www.mhra.gov.uk, which went live 7 January 2012. The new homepage presents the latest information, including safety updates, in a clear, user-friendly fashion. There are clear ways to navigate to whatever information you need from the website and links to browse through sections. The development of the new home page has been based on user feedback, including a website survey conducted over the summer. Feedback on the new home page can be sent to webusability@mhra.gsi.gov.uk.

North/South America

Canada

Health Canada Issues Consultation on "Draft Guidance on Classification of Observations for Inspection of Cells, Tissues, and Organs Establishments"[14]

This document is an administrative tool and is intended to:

- Assist in the classification of observations made during inspection of Cells, Tissues, and Organs (CTO) establishments.
- Promote uniformity in the assignment of ratings to individual observations and to overall inspection ratings of the CTO establishments.
- Provide examples of situations of non-compliance with the Safety of Human Cells, Tissues, and Organs for Transplantation Regulations.

To view the document, visit http://www.hc-sc.gc.ca/dhp-mps/consultation/compli-conform/2011-gui-0101_doc-eng.php.

Health Canada Issues Consultation on "Cleaning Validation Guidance"[15]

The Cleaning Validation Guidance provides some guidance on issues and topics related to validation of equipment cleaning for the removal of contaminants associated with previous

products, residues of cleaning agents as well as the control of potential microbial contaminants for pharmaceutical, biological, and radiopharmaceutical products. Utilization of this information should facilitate compliance with Division 2 Part C of the Food and Drugs Regulations. This guidance document was revised to reflect the current regulatory environment and to add an Appendix which provides concrete examples of cleaning calculations to establish maximum allowable carryover limits based on therapeutic dose.

Health Canada Issues Consultation on "Draft Guidance on Process Validation: Terminal Sterilization Processes for Pharmaceutical Products"[16]

The draft guidelines outlined in Guidance on Process Validation: Terminal Sterilization Processes for Pharmaceutical Products (GUI-0074) apply to the validation of sterilization of raw materials, packaging materials, and finished products for pharmaceutical and veterinary drugs. This guidance was revised to reflect the current regulatory environment and to clarify certain aspects that have relevance to the validation of terminal sterilization processes.

United States

US FDA Develops Regulatory Site Visit Training Program[17]

The Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) has developed a Regulatory Site Visit Training Program (RSVP) and they are looking for participants. This training program is intended to give CBER regulatory review, compliance, and other relevant staff an opportunity to visit biologics facilities. These visits are intended to allow CBER staff to directly observe routine manufacturing practices and to give CBER staff a better understanding of the biologics industry, including its challenges and operations. FDA invites biologics facilities to contact CBER for more information if they are interested in participating in this program.

US Government Accountability Office Comments on FDA's Drug Labels[18]

The US Government Accountability Office (GAO) found that the FDA has not taken sufficient steps to ensure that antibiotic labels contain up-to-date breakpoints. The FDA designates certain drugs as "reference-listed drugs" and the sponsors of these drugs play an important role in ensuring the accuracy of drug labels. Reference-listed drugs are approved drug products to which generic versions are compared.

As of November 2011, the FDA had not yet confirmed whether the breakpoints on the majority of reference-listed antibiotics labels were up to date. The FDA contacted sponsors of 210 antibiotics in early 2008 to remind sponsors of the importance of maintaining their labels and requested that they assess whether the breakpoints on their drugs' labels were up to date. Sponsors were asked to submit evidence to the FDA showing that the breakpoints were either current or needed revision. As of November 2011, more than 3.5 years after the FDA contacted sponsors, the Agency had not yet confirmed whether the breakpoints on the labels of 70 percent or 146 of the 210 antibiotics were up to date. The FDA has not ensured that sponsors have fulfilled the responsibilities outlined in the early 2008 letters.

For those submissions that the FDA has received, it has often taken more than a year for the FDA to complete its review. Officials attributed this delay to reviewers' workload, challenging scientific issues or difficulties in obtaining needed data, and incomplete submissions. The FDA also issued guidance to clarify sponsors' responsibility to evaluate and maintain up-to-date breakpoints. The guidance reminded sponsors that they are required to maintain accurate labels and stated that certain sponsors should submit an evaluation of breakpoints on their antibiotic labels to the FDA annually. However, the FDA has not been systematically tracking whether sponsors are providing these annual updates. Some sponsors remain confused about their responsibility to evaluate and maintain up-to-date breakpoints. At GAO's request, the FDA reviewed a small sample of annual reports and determined that few sponsors appear to be responsive to the guidance.

The Food and Drug Administration Amendment Acts of 2007 (FDAAA) provisions related to antibiotic innovation have not resulted in the submission of new drug applications for antibiotics. FDAAA extended the period of time that sponsors of new drugs that meet certain criteria have exclusive right to market the drug. According to FDA officials, the Agency has received very few inquiries regarding this provision, and as of November 2011, no new drug applications for antibiotics have been submitted that would qualify for this exclusivity. None of the drug sponsors GAO received comments from said that this provision provided sufficient incentive to develop a new antibiotic of this type. FDAAA also required that the FDA hold a public meeting to discuss whether and how existing or potential incentives could be applied to promote the development of antibiotics. Both financial and regulatory incentives were discussed at the FDA's 2008 meeting, including tax incentives for research and development and providing greater regulatory clarity during the drug approval process.

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