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Using Technology Transfer to Maximize Business Efficiency

by Russ Somma, PhD

This article presents a technology transfer approach that can help prevent costly delays, leverage the ability to change, and speed time to market.

Introduction

In today's highly competitive marketplace, pharmaceutical companies must use their resources wisely. Often this means outsourcing production to other sites, both in the United States and abroad. As a result, successful technology transfer is more critical than ever.

Achieving success requires a paradigm shift. Traditionally, technology transfer teams were charged with moving a physical process from research and development into production. While that role remains critical, today's transfer team plays a larger part, helping the company attain its strategic goals throughout the product lifecycle. Systematically managing and sharing knowledge, prior to and during the technology transfer process, can help speed market entry. A scale-up operation is useless unless it can be leveraged in a business environment. From their vantage point near the end of development, as the product enters into commercialization, the transfer team is strategically positioned to capture information and provide feedback that can result in better market readiness - *Figure 1.* By sharing that information, the team can help the company begin the rise to peak sales. It is helpful to think of technology transfer as a knowledge transfer process – and to remember that it is not a stand-alone process, but a component in the drug development continuum.[22,26]

This article examines some of the elements – including development of a knowledge store and minimizing process complexity – that help elevate the technology transfer process to a strategic tool that can maximize business efficiency.

The Importance of Shared Knowledge

"Continuous improvement" is not just a buzzword; it's a business practice. The more effectively knowledge is shared within an organization, the more efficiently the organization can operate. However, too often, information is gathered but not shared, and so it is limited in its usefulness.

Continuous improvement is possible through *incremental knowledge*. Incremental knowledge is gained through ongoing activities, and it grows with each transfer project. It can be as specific as the location of the new manufacturing facility or as broad as the idiosyncrasies of the production process. Incremental knowledge provides a basis for rethinking business processes as knowledge changes. Continually building on the existing body of information improves the quality of handbooks and Standard Operating Procedures (SOPs), reduces uncertainty, and moves the collective knowledge base forward.

As the body of incremental knowledge grows, the new information may then become *explicit knowledge* – that is, knowledge that can easily be set down in procedures, handbooks, or process maps. At the other extreme, *tacit knowledge* is not easy to codify or communicate. It is, simply put, "having a feel for the process." It may be, for example, an individual's knowledge that a process cannot run on certain days of the week due to manpower shortages. The goal is to build the store of explicit knowledge, because it is easily transferable. Such a "knowledge store" could include proven acceptable ranges for the production process as well as a manufacturing facility's specific capabilities – any information that the company might need to access quickly at any point in the product lifecycle.

Explicit knowledge is not an exotic concept - it is the information that pharmaceutical development deals with every day: robust formulations, meaningful specifications, etc. Because it can save valuable time, explicit knowledge is cost effective. It results in a well-defined set of core technologies, speeds development and process introduction, and should serve as the basis of the team's work. The goal should always be

to minimize tacit knowledge and enhance the explicit knowledge base, using incremental knowledge to continuously improve processes.

Knowledge transfer within a company can be called "organizational learning." Traditional means – such as handbooks, policies, SOPs, and even e-mail – can facilitate organizational learning, but additional means must be considered in order to share knowledge most effectively. Information technology tools such as groupware can facilitate knowledge transfer by combining, categorizing, and organizing information and making it available across teams.[1,2,3,4] To the degree possible, team members should meet face to face. Although this approach is not inexpensive, it may pay for itself in time savings, as potential issues surface readily and can be addressed promptly. For the same reason, consider assigning staff to the target transfer sites for process introduction.

The technology transfer team should represent all stakeholders, from development to engineering to production. Again, this is not a radical concept. Certain companies use cross-functional project teams or Chemistry, Manufacturing, and Controls (CMC) teams during the development process to bring all product knowledge, including clinical aspects, into one cohesive unit. The transfer team must take the same approach, as no one person knows everything necessary to prepare a product for market entry. The task is simply too complex. Although the clinical aspect may be out of scope here, the technology transfer team should include professionals representing supply chain management, packaging, and health and safety. In fact, consider consulting all disciplines that would ordinarily be needed to maintain a product on the market. However, the objective here is not to bring together a large, ineffectual team, but rather to form a focused group of point people who are supported by a well-chosen support network. Key members should represent tasks that are technically associated with the product. A secondary resource group can include those who play supportive roles during the product lifecycle and who can address most scenarios that the core transfer team is likely to encounter. Identifying these resources at the outset gives the transfer leader the ability to quickly address any hurdles that arise along the road to market entry. For example, some companies have selected market packages that were not known to all stakeholders in the supply chain, placing the outcome of the transfer at risk and missing tight timelines. A multidisciplinary team that systematically shares knowledge can help prevent such potential obstacles. The team creates the knowledge store – a resource to which all may turn for direction.

Remember that learning occurs not only within teams and across teams, but from the market. The importance of market learning – gained by monitoring competitors via industry news and regulatory citations – should not be overlooked. For example, take the company working on a bilayer tablet formulation. The knowledge that a competitor faces regulatory action due to delamination on a similar formulation is a critical piece of business intelligence. The information should drive the company to modify its approach to the outlining of the product's quality attributes. Critical analysis of the information might even direct the company to adopt unique in-process controls.[11,17, 21]

Start Early to Build a Robust Knowledge Store

Ultimately, the knowledge store – explicit, optimized knowledge of the product and processes – drives successful technology transfer by reducing uncertainty and accelerating the transfer process. What elements should the knowledge store include? How should it be developed?

Compile data as early as possible in the development cycle and use it to establish a technology strategy that will qualify change in the context of scale-up or site transfer, as well as possible post-approval changes. This approach can speed both product development and product approval. Be sure to focus on data that protects the patient, i.e., critical quality attributes, and assures that the process is under control, bearing in mind that the two are not necessarily related. For example, with a high-dose tablet, nine times out of ten, the assay is not as important as the weight. Depending on the dosage form, the drug substance and its Biopharmaceutical Classification System (BCS) classification, creating an *In Vitro*/*In Vivo* Correlation (IVIVC) may benefit formulation and process optimization and the creation of meaningful specifications. Investing time and money to establish IVIVC will allow the company to move quickly without having to conduct subsequent human kinetic studies prior to technology or site transfer, ultimately shortening time to market.[6,10] Of course, the IVIVC will be specific to the formulation, and thought must be given to where in the development cycle IVIVC will be established.

To establish the IVIVC early in the process, use blood profile data from "discovery phase" studies as a starting point for dissolution work. Even if it is from animal studies, it provides a direction. As the formulation is optimized, continually refine and validate the data and add it to the knowledge store. During scale-up, the dissolution data can be used to judge the impact of process changes as well as to establish final specifications for dissolution. Anchoring specifications to human kinetic data provides reliability and a guidepost to make defendable changes regarding the site or the process.

However, be aware that the use of a sound pharmacokinetic basis for setting specifications and establishing a reproducible process alone is no guarantee of success. For example, one company was producing a modified release product. The product passed an US FDA Pre-Approval Inspection (PAI) with no issues, only to have a commercial manufacturing failure rate of 10% at maximum output. Three batches were produced for the PAI with no problems, but at high output, the process disrupted the product's polymeric coating, and the product failed to meet critical quality attributes. Availability of explicit knowledge concerning the method of handling the bulk product would have prevented this problem. In this case, a champion from the launch site at an early stage to help other team members understand the commercial implications would have been the best way to grow the knowledge store.

To continue building the knowledge store, use process development as a platform to establish proven acceptable ranges. Doing this provides a historical database for the product and a basis for statistical process control. Companies that fail to develop and systematically catalog proven acceptable ranges often stall in a pre-approval inspection, because they cannot readily access the information necessary to answer the FDA's questions – even if the information exists.

Start with broad ranges during early development and revise and refine them through Phase I and clinical trials. Use a systematic reporting method and reference it with every change from pilot scale, through scale-up and validation. Simple tabulations at the beginning of process development will prevent huge problems later.[23]

To establish proven acceptable ranges, create a chart for all process steps and controllable parameters, along with a brief description of each. Record the engineering units, and document the anticipated result of exceeding the proven acceptable range. Evaluate whether the risk of exceeding the range is major or minor. It is minor if it represents no risk to the patient. Documenting this risk assessment serves as a "bulletproof vest" by backing up the information in the primary documents, such as product development reports, justification of specifications, and validation reports. For each parameter, establish the operating range to be used in the plant for process control. Acceptable ranges that depend on scale changes, such as the number of spray guns or fluid bed dryer air volumes, can be listed as "to be determined."

As a final step in building the knowledge store, completing technology transfer through validation may be an expedient way to assure rapid market entry. Just to be clear, all facilities, equipment, and critical systems must be fully qualified before executing any product validation. Validation demonstrates control over the process and finished product, ensures compliance with internal and external requirements, and adds to the knowledge store. Bearing in mind the Quality by Design initiatives and the guidance of ICH Q8 and Q9, the manner in which the company is going to file will determine the nature of the validation. However, for the foreseeable future, the majority of filings are likely to follow the three-batch validation paradigm. Regardless of whether the company files a currently accepted submission or opts to adopt Quality by Design, creation of a solid knowledge store is imperative – and grounded in current industry practices. Ultimately, the forward-looking approach necessary to build a knowledge store will support a company's adoption of Quality by Design, which is firmly rooted in knowledge management.

Although not required, completing validation prior to a submission may expedite market launch. While this view may not be acceptable to generics companies, small companies with limited drug substance supplies, and others who do not include validation in their business plans, validation is one step in the journey to 100% business efficiency and peak sales.[9,21] If a process and product are already validated, production can launch within two days of registration approval; otherwise it might take six to nine months to ramp up production. In that time, the competition might already have gained a large share of the market. To assure a rapid path to validation, use a risk-based approach that balances good science and common sense. Rate each process step as having a high, low, or no impact on product quality.[7] For clarity, use Scale-Up and Post-Approval Changes (SUPAC) equipment terms. For example, the critical area checklist for a film-coated tablet may include:

- Weighing/addition of raw materials
- Pre-blending of materials
- Granulation (speed, rate of addition, time)
- Drying (temperature, time)
- Particle size reduction
- Blending/lubrication
- Compression
- Coating

Record data related to the items on the critical area checklist and review them for traits and atypical behavior. Showing the data graphically makes it easier to identify process variability within established specifications, in other words to compare processes.[5,8] Defining these critical areas, their endpoints, and their impact saves time and effort when designing the validation strategy and the process parameters going forward. Once the information is compiled, it is possible to look at expected parameters and atypical behavior, and then identify realistic ranges for statistical process control during the product lifecycle.

As the new drug development clock ticks, the Pre-Approval Inspection (PAI) is clearly a key milestone - but it does not stand alone. The largest strategic mistake a company can make is to think of development, regulatory submission, transfer, and PAI as separate and unrelated events. A good transfer team ensures that all these aspects are addressed clearly and logically in a deliverable that is consistent with the regulatory submission. If the team has followed the approach outlined here, capturing and sharing explicit knowledge from the early stages of product development, then the team will be prepared, and the transfer and subsequent PAI become steps in a seamless continuum that lead toward market dominance.

During the PAI, the FDA investigators look at drug substance characterization, process procedures, in-process tests, finished product specifications, dissolution profiles, and stability.[12] If the launch site is detached from the development site, the investigators may audit both. If the knowledge store has been well defined, the information that the investigators need is readily available. Any issues that arise can be addressed quickly. Having the product information recorded and available during PAIs will prevent delays and expedite product launch. The other key advantage of a well-developed, well-utilized knowledge store is that it can facilitate communication between the transfer and the CMC teams. This helps ensure that the inspection is seamlessly aligned with the regulatory submission – so the reviewing chemist sees the same information as the field inspector does.

How to Share the Knowledge Successfully

Building a knowledge store can provide significant benefits throughout the technology transfer process and beyond – but only if the knowledge is shared and utilized. Whether the product is being transferred to an existing group company, a contractor for custom manufacturing, an established company through collaboration, or to an expansion facility, two things are vital: good communication and a streamlined technology transfer process.[20,24]

The technology transfer team is charged with getting from A to B in the shortest time possible so this is no time for complicated studies. To minimize process complexity, establish the *same process technology* at all manufacturing sites. For example, it would not be advisable to attempt to go from high-shear in a bottom-driven machine to high-shear in a top-driven machine without considering the full impact and possible downside. In those considerations, team members must look beyond their specific activities. Establish a common technology agreement between the launch or production site and the development area and integrate the agreement into the transfer strategy. This will accelerate process introduction and enhance core capabilities. It also makes it possible to source Phase III supplies.

Wherever possible, combine efforts such as site qualification and operational qualifications data for the process; use the final market image. As noted above, avoid radical process changes, and use the SUPAC equipment guide to establish sameness of equipment and process. Develop processes using a sub-batch concept. For solid dosage forms, this reduces validation and supplies a defendable basis for change in scale. For example, in a wet granulation process, granulate in two sub-batches and then blend out in one. For scale up, change the size of the blender with a commensurate change in the number of sub-batches.[15,16]

Remember that technology transfer is an "away" game that is likely to be played out in an environment with different rules. It is important to know the culture of the transfer site. Each organization, and each site, has an integral pattern of behavior and thinking, a way of doing things that makes perfect sense to that particular group. An aberration – such as a speck in the color – that one culture, e.g., the sponsor, might consider a minor variation, might be viewed by the other (e.g., the contract manufacturer) as a reason to stop the batch. It is important to establish upfront whose philosophy will dictate the manner in which the batch will be processed. These cultural discussions should not be adversarial, but they should be held early. There should be a two-tiered approach – one is the contractual agreement and the other is the daily working agreement. Agreements must be shared with all transfer team members.[13,14,18,19,25]

Prior knowledge of the infrastructure also is important, especially if production is transferred to another country.

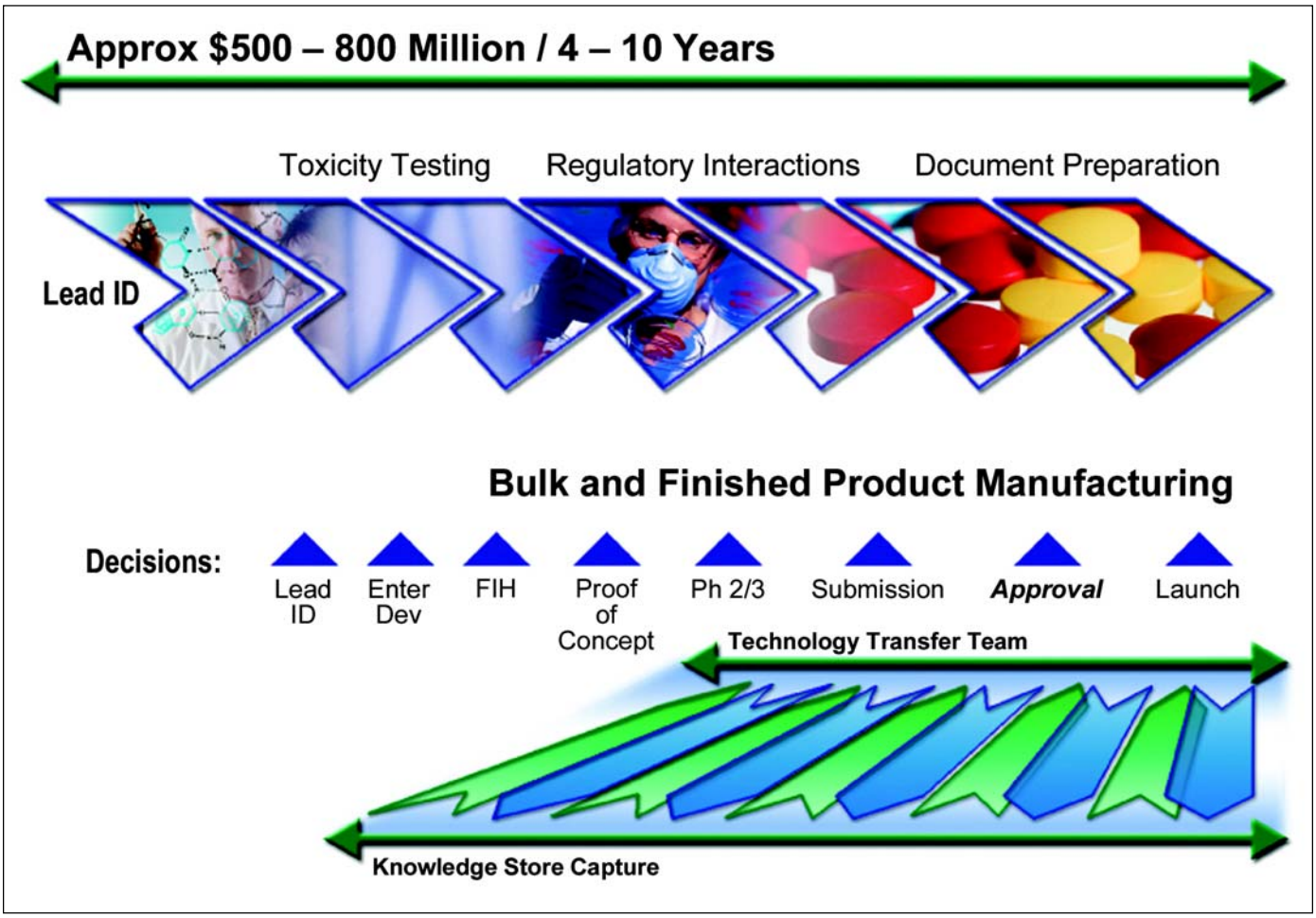

Figure 1. Drug development and technology transfer.

Ensure that the supportive infrastructure extends beyond Quality Control (QC) and Good Manufacturing Practices (GMP) to include a range of other crucial factors that cannot be taken for granted. Otherwise, the project may be headed down a path to disaster, regardless of whether the product is a tablet or a semi-solid. For example, does the site have potable and purified water? Most pharmaceutical engineers have encountered facilities that shut down during certain times of day because there is no water. Does the site have adequate steam pressure and capacity? Does the dryer work within our desired range? Can two dryers run simultaneously? What about Heating, Ventilation, and Air Conditioning (HVAC)? Don't assume that the availability of air conditioning means that the facility is cooled 24/7. A building that is only air conditioned Monday through Friday is not a good choice for production of a product that is affected by heat. Is the waste management infrastructure adequate for the manufacturing capacity? In one recent scenario, the transfer team inspected the transfer site, observed floor drains and assumed that waste would be adequately handled. After introducing the product, the transfer team returned to the site and observed that wastewater was being drummed. They found that the effluent amounts exceeded the treatment plant's capacity. The company was now financially obligated for a $15 million waste treatment facility upgrade, a cost that was certainly not part of the initial plan. The transfer team was at fault, as no one had asked the key questions during the initial site visit. Clearly, lack of knowledge can lead to disastrous consequences.

Other factors that may hamper successful transfer of product include insufficient labor pool, inaccessibility of the plant, registration with local agencies, and communication and language barriers. In a validated environment, a smile and a nod are simply not adequate communication. It also is critical to establish what would happen in the case of a business interruption due to a facility disaster such as fire or explosion. Is the facility covered for these scenarios and who is liable?

Finally, while it is not always feasible to assign a team member to the transfer site, do it whenever possible. As noted above, nothing is more important in a successful technology transfer than on-site inspection of the facility and face-to-face communication with the team.

Conclusion

The essence of technology transfer is transferring the knowledge and understanding of the process from one site to another. It is not an end in itself, but part of a larger process that begins with product development, assures business efficiency and peak sales, and follows the product throughout its lifecycle. Along the way, building a knowledge store that can be refined and shared allows for continual improvements and facilitates technology transfer. To develop this knowledge store, it is necessary to minimize tacit knowledge and maximize codifiable explicit knowledge. Begin to build the knowledge store during early development, and refine it with lessons learned from internal processes as well as competitor and market information.

In addition to gathering data and documenting the product and process, it is important to know a great deal about the transfer site. Discuss each site's culture and agree as to which will be the driver, and wherever possible, plan for site visits and face-to-face meetings.

The additional time and effort involved in the approach described here can not only facilitate technology transfer, but can help prevent costly delays, leverage the ability to change, and speed time to market.

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Russ Somma, PhD has 30 years of pharmaceutical industry experience and possesses expertise in the areas of production troubleshooting, dosage form development, manufacturing scale-up, technology transfer, and Quality by Design. He has provided support for 21 NDAs in the chemistry, manufacturing, and control area from submission through the pre-approval inspection phase. As president of SommaTech, LLC, his focus is on pharmaceutical technology and helping clients achieve their US FDA regulated product goals and assuring a cost effective product and a secure supply chain. Somma is the Chair of ISPE's Product Quality Lifecycle Implementation (PQLI) project, Chair of the ISPE Professional Certification Commission (ISPE-PCC), and past Chair of ISPE's SUPAC Equipment Guidance Steering Committee. Somma is a "Hammer Award" winner, presented by Vice President Al Gore's Committee for National Performance Review. He can be contacted by telephone at: +1-732-748-1990 ext. 203 or by e-mail at: rsomma@sommatechconsulting.com.

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Technology Transfer as a Strategic Tool: Bridging the Valley of Death

by Jeff Odum

This article was developed from the presentation "Technology Transfer: Implementing Current Best Practice Guidelines to Manage Risk" presented at the ISPE Conference in Paris, 2007.

"The Valley of Death." This does not sound like a fun place to be, yet alone to try and do business in. But the image of such a place is one that many companies must conquer in order to maintain their competitive advantage or to enter the marketplace with new products for an ever-demanding consumer marketplace.

The concept of the "valley of death" has become a visual icon to describe the difficult task of successfully implementing new and/or proven technologies that leads to the commercialization of products. Companies and organizations, from the Defense Department to start-up companies, have found that understanding, managing, and implementing successful programs to transition technology are valuable strategic resources. This act of transitioning technology that we refer to as technology transfer is more than just the transfer of a product and/or a manufacturing process. It is a key tool in a company's strategic operations that must be understood in order to be effectively managed.

Like any project, technology transfer involves many people, groups, forms of documentation, and in some instances, a number of different organizations. It is critical to the manufacture of a pharmaceutical product that those involved in the manufacturing effort have access to the most relevant and up-to-date information. Therefore, technology transfer is a process for ensuring that this information is available when and where required. It also must be viewed as a wide set of processes that manage the flow of knowledge, experience, data, and equipment between the sending and receiving organizations that must lead to an actual demonstration of transfer.

What is Technology Transfer and Why is it so Difficult?

In its simplest form, technology transfer is viewed as a two-way exchange. Even if the technology is moving in one primary direction (such as from a R&D lab to a commercial manufacturing entity), there will be two or more parties participating in a series of communication exchanges as they seek to learn and find common ground regarding the meaning of the technology and the attributes of the product. So it can be clearly seen that technology transfer is really a back-and-forth communication process that can involve a large number of resources. In the book *Diffusion of Innovation*, Everett Rodgers concludes that, "technology transfer is difficult, in part, because we have underestimated just how much effort is required for such transfer to occur effectively."[1]

Death Valley.

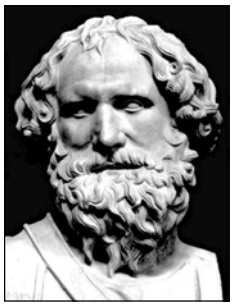
So we must view technology transfer as a form of partnership, whether it is an internal activity or one that involves resources outside of our corporate structure. So how should we define technology transfer? It is the formal transfer of product (formulation and pack-

age), process, and analytical methods from development laboratories to manufacturing operations for the purposes of launch of commercial quantities of finished product meeting all cGMP attributes, including safety, identity, strength, purity, and quality.

But there is more to successful technology transfer than just the right flow of data and information. There are other dynamics that must be recognized and addressed that have a significant impact on success.

Dynamics in the Culture of Innovation

Technology transfer is not some recent phenomena tied to the industrial world we live in. Archimedes is known as one of the first practitioners of technology transfer through his efforts to apply science to the practical problems of his time.[2] Today, many of the problems that companies face in executing successful technology transfer activities come about due to cultural differences that may be as pronounced as those faced by the ancient Greek scientist.

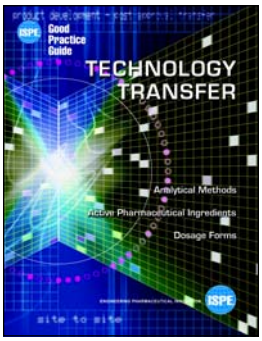


Archimedes.

Corporate culture can play a significant role in technology transfer. Companies that have very rigid, hierarchical organizations find the technology transfer process may be hindered when rules and policies hinder the flow of information and communication. Short-term planning focused on economic concerns is not efficient. Leadership from upper management may not communicate a sense of urgency to succeed and clearly define a "champion" for the technology transfer effort. Rigid job descriptions, internal procedures, and the mentality of "doing things our way" can kill the effort.

So what are some of the positive characteristics to foster innovation? *Flexibility*. Change is a given. Adjusting tasks through interaction is critical. *Commitment*. People must be committed to succeed beyond just doing their job. The commitment has to go beyond defined functional roles if it is to be strategic in its execution. *Communication*. The flow of information exchange must be unhindered across the organizational hierarchy. *Creativity*. Thinking outside the box and showing originality should be encouraged, not suppressed.

Technology Transfer in the Pharmaceutical Industry



The ISPE Good Practice Guide on Technology Transfer was published in 2003. In this document, technology transfer is viewed as the embodiment of the transfer of documentation and the demonstrated ability of a Receiving Unit to effectively perform the critical elements of transferred technology, to the satisfaction of all parties and any or all applicable regulatory bodies. And simply stated it is considered a success if the Receiving Unit can routinely reproduce the transferred product, process, or method against a predefined set of specifications as agreed with the Sending Unit and/or Development Unit.[3]

From a regulatory perspective, the success factors for a successful transfer of technology include:

- The presence of an acceptance criteria or specification
- Establishment of adequate facilities and trained staff
- Establishment of protocols and standard operating procedures
  - Agreed upon plan for transfer
- Data
  - Evidence that process was successfully reproduced

And to be deemed successful, the transfer process also must result in:

- A safely completed effort
- The process being transferred runs as advertised (yield, purity, cycle time, etc.)
- On time completion
- On budget completion
- No "crisis" situations occurring

Technology transfer is not a unique one time event. From research to commercial production, there are many times when a transfer activity will be required, along with a number of reasons for the transfer of information - *Figure 1*. Each stage of technology transfer will involve a different type of transfer process, rationale for the process, and set of personnel resources. There also will be a number of different scenarios that can occur that define the Sending and Receiving Units. These include:

- Idea to Discovery Lab
- Discovery Lab to Development Lab
- Development Lab to Kilo Lab
- Lab to Pilot Plant
- Kilo Lab to Pilot Plant
- Pilot Plant to Semi-works (other Pilot Plant)
- Pilot Plant/Semi-works to Manufacturing
- Manufacturing to Manufacturing

Technology transfer also must be treated as a key component of operational strategy. Without repeatable and scalable manufacturing processes, companies will find themselves falling into the trap of "reinventing the wheel" every time technology changes hands within their organization. Therefore, it makes sense that technology transfer should be seen as a core competency within the corporate structure, much like manufacturing, quality control, logistics. The focus of such a competency should include reducing transfer cycle times, maximizing efficiency by reducing redundancy and costs, improved quality, and a reduction in compliance issues and regulatory observations.

The process of technology transfer involves a number of

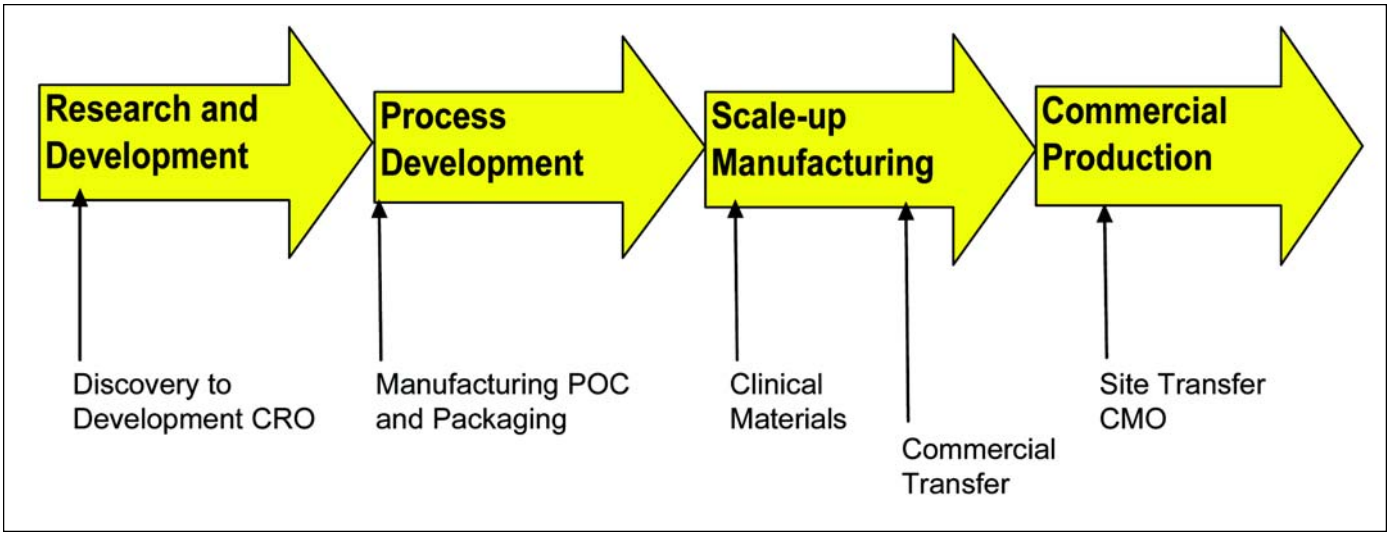


Figure 1. Stages for technology transfer.

key elements. These can be described in basic project management terms as:

- Formation of a team
- Establish good communications
- Set objectives
- Good documentation
- Knowledge transfer
- Analytical methods transfer

Formation of the Team

Right team, right results. Team make-up and chemistry is so important. Sending and Receiving Units should not be established and managed as two separate groups; they are one Team, even though they may be part of two different organizations.

Understanding roles and responsibilities is critical to the success of any project team. Defining boundaries of responsibility also is important. Overlapping responsibilities, duplication of activities, or the failure to define execution responsibility can be disastrous. A simple, yet effective tool can be implemented between both units to define roles and responsibilities.

RACI charts are a proven project management tool. RACI is an acronym for:

- **R** Responsibility: who is responsible for the execution of the task
- **A** Accountability: who is responsible for seeing that the work is completed
- **C** Consulted: who are the people that should be consulted in decision making
- **I** Informed: who needs to be informed

A sample diagram template is given in Figure 2.

Management buy-in also is essential. There also should be a "champion" with sufficient authority to remove road-blocks, generate support, and ensure successful implementation of the execution approach. People must be empowered to take risks and know that failure is anticipated along the way, because failure can provide valuable lessons.

Communication

Another key project management activity that the technology transfer Team should execute is to develop the project plan, one of the most critical elements of communication. This document will serve as the road map across the "valley of death" and must be clear, thorough, and well-defined.

The project plan should include a clear definition of the project that states objectives and deliverables. Quality standards, schedules and milestones, resources, and documentation requirements also must be addressed. The plan also should define a key task list. This will include:

- Team organization (resource definition)
- Assessment of facilities
- Health, safety, and environmental assessment
- Skill set analysis/training
- Process development/approval
- Analytical method transfer procedures
- Raw material component evaluation
- Supply quality definition
- Equipment selection and transfer

Assigning Roles and Responsibilities – The RACI Chart

Project:		Date:			
Names / Activities	Name A	Name B	Name C	Name D	Name E
Activity A	R	A	C	I	
Activity B	R		I		
	I	R		C	
	I	R		C	

R-Responsible A-Accountable C-Consulted I-Informed

Figure 2. RACI diagram format template.

- Process transfer
- Verification
- Data review
- Conclusion reporting/sign-off

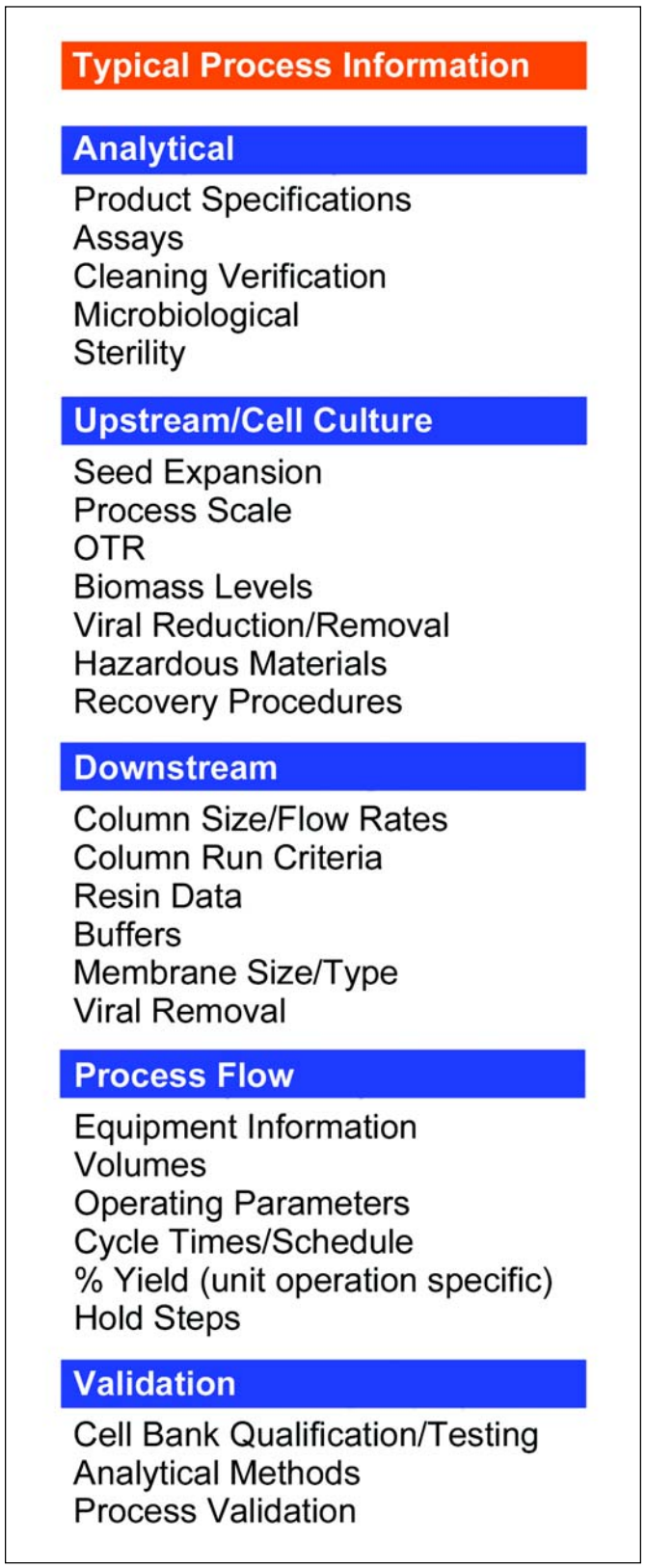


Figure 3. Typical process transfer information.

Objectives

Technology transfer can encompass a wide range of transfer activities. The objective of these activities should be clearly defined by all parties. But more important, the definition of success for the technology transfer and the acceptance criteria must be understood.

The purpose of acceptance criteria will be to demonstrate that the process performs as defined in the project plan and that it produces the drug product per the defined product characteristics. Acceptance criteria will depend on the condition of the process at the beginning of the transfer. Processes that are not as well-defined (pre-clinical candidates or clinical materials) will have less exact criteria than that of a commercial product being transferred. But remember that technology transfer rarely occurs without some unexpected issues. Flexibility and a gradual implementation approach will reduce risk.

Remember that technology is really information that has been proven correct.

Documentation

The leading source of problems in a technology transfer effort is failing to understand the quality of the information being transferred. In an ideal world, all the information being transferred is true and accurate. But in practice, the information is in reality, a mixture of knowledge, technology, and beliefs. If the transmitted information is clearly labeled as beliefs, then the recipient can convert beliefs into technology via experimentation. In many cases, the Sending Unit may not have the tools to develop all of the ideas and beliefs into technology.

Some of the more common types of information are shown in Figure 3.

Knowledge Transfer

Knowledge is thought to be true based on experimental results or observations. It is generally held true by the developer of the information. Knowledge is generally created from minimally controlled, single point experimentation using protocols, careful experimental technique, and is well documented.

It is critical to the manufacture of a pharmaceutical product that those involved in that manufacture have access to the most relevant and "up-to-date information" (and knowledge). Technology transfer is the process for ensuring that this information is available "when and where required" (and a mechanism to ensure we convert this information into institutional knowledge and memory to ensure continuous improvement).

The transfer of knowledge is continuous. It begins with the technical details of the process and the product. It involves the transfer of experimental data from the lab. It moves into pilot scale operations, sometimes in more than one location. And it must include on-site support during start-up. Knowledge transfer also requires a mind-set of continuous improvement. The adoption of a continuous improvement model will help define metrics and link them to risk mitigation. It will

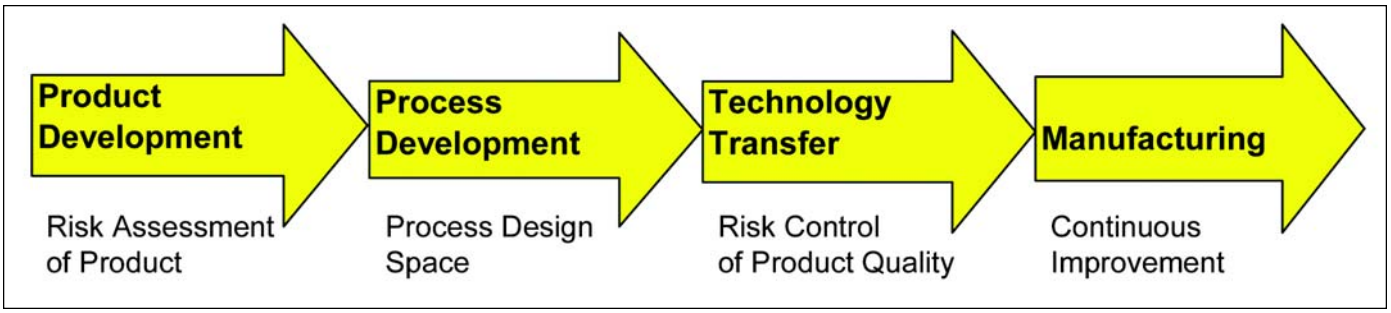


Figure 4. Risk management through the product lifecycle.

improve the ability to "hear the customer" and improve communication. And it will create feedback mechanisms for learning, improving efficiency, and risk reduction.

Analytical Methods Transfer

All methods for testing a given product, ingredient, or sample must be developed and transferred to the Receiving Unit. The method in which the Receiving Unit receives this data should be qualified. The transfer of this data should occur before the execution of the transfer protocol. This will allow for review and discussion between the Sending and Receiving Units before physical work begins.

The transfer protocol includes the following key parameters and acceptance criteria for each analysis:

- Reproducibility
- System precision
- Selectivity
- Detection limit
- Quantification limit
- Linearity and range

The Cost of Failure

The business libraries are full of works written about failures in technology transfer and the disastrous consequences that companies experience due to their failure to treat technology transfer as a strategic tool. In his book, *Mastering the Dynamics of Innovation,* James Utterback writes: *"A critical pattern in the dynamics of technological innovation…is the disturbing regularity with which industrial leaders follow their core technologies into obsolescence and obscurity."*[4]

The failure of the Xerox Corporation to commercialize most of the innovations in computer technology developed by their Palo Alto Research Center (PARC) is one of the most famous examples of failed technology transfer.[5] PARC was focused on developing the "office of the future." The technologies developed by PARC included the world's first personal computer, the mouse, local-area networks, and laser printing. Only laser printing was commercialized by Xerox. One of the primary reasons for this failure was that Xerox did not have an effective method or defined mechanisms in place to transfer the technology from the R&D effort to manufacturing.[6]

Companies that define technology transfer as a core competency will have shorter, more efficient transfer processes that will save time and money. The collaboration between individuals and groups will foster communication and reduce risk. Speed to market will be improved. Identification of regulatory hurdles can be evaluated well in advance of launch. Marketing will have an opportunity to understand the new technology/product in order to better develop a strategy for launch.

The Future

There are a number of significant initiatives within the industry that will have significant impact on the execution of technology transfer. The industry view of Quality by Design (QbD) is focused on the transfer of knowledge, understanding that knowledge, and using this knowledge to improve process and product efficiency and quality. The focus is on managing risk, and can be viewed in terms of the "flow" through the product lifecycle - *Figure 4*.

The future focus of technology transfer efforts will include establishing the design space for the product and the true definition of the desired state of product quality. This is where the implementation and understanding of the ICH documents, including Q8 (Pharmaceutical Development) and Q9 (Risk Management) will become imperative. If there is agreement on the view that the main objective of technology transfer is to confirm the suitability of the process and to streamline its transfer into manufacturing, then managing operating risk while maintaining the GMP definition of "state of control" will add new challenges to managing the technology transfer effort.

While technology transfer is a strategic effort, it is by no means a static activity.

Conclusion

Technology transfer is a challenge. It should be viewed as a strategic tool that can have a tremendous impact on costs and market penetration. The essence of technology transfer is communication. It is not a one-time event that involves one-way communication. It is a long-term commitment to dialogue between the Sending and Receiving Units that should be treated as a partnership.

Bridging the "Valley of Death" requires an understanding of the tools necessary to make the journey. Management must create a culture that fosters both innovation and communication. Some failures will occur, but they should not be viewed as the death knell to a product or program. Failures are opportunities for lessons learned and should be used to foster innovation, not hinder it.

The promise of new medications and therapies is endless

in the pharmaceutical industry today. Technology transfer will play a key role in how these new products reach the consumers, when it occurs, and how the costs will be assessed. In the end, technology transfer can be the driving force that brings discovery to the marketplace.

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About the Author

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Small-Scale Bioreactor Platform for Bioprocess Optimization

by Marisha Ben-Tchavtchavadze, Michel Perrier, and Mario Jolicoeur

Introduction

The discovery of recombinant DNA technology has changed the face of the pharmaceutical industry in the last 20 years due to the introduction of the large-scale bioprocess production of therapeutic proteins. It has become such an invaluable technique that the use of microorganisms and mammalian cells to produce therapeutic metabolites and proteins is estimated to increase by approximately 50% over the next five years, making it into a $53 billion industry by 2010.[1,2] This trend is far from surprising due to the opportunity to discover and produce new therapeutic targets with tools such as metabolic engineering. This dedication to increase biopharmaceutical production also has become critical to assure that the demand of needy patients does not surpass availability and is not only of important commercial value, but also of great social value.

Recombinant protein production is accomplished by the use of several different expression systems such as bacteria, yeasts, plant, insect, and mammalian cells. Although bacteria and other prokaryotic microorganisms have the advantage of producing high protein yields and production costs are relatively low, they do not possess the cellular machinery to perform post-translational modifications, such as glycosylation, essential for the production of many biomedically active proteins. Therefore, eukaryotic cells such as plant or mammalian cells are preferred when glycosylation is critical for bioactivity. While the large-scale production of human proteins by plant cells is increasing in interest,[3] most biopharmaceutical processes in the industry employ free-suspension mammalian cells due to their lack of cell walls which makes recovery and purification simpler.

Bioprocesses aim to manipulate and control cell lines to attain the maximum product yield and productivity at the lowest cost and in the most efficient way. Even though bioprocesses using mammalian cells have progressively achieved increased production yields at reduced costs, there are still many hurdles to surpass to fully optimize their recombinant protein production. Mammalian cell cultures are still reporting lower cell densities than microbial cultures for example.[4] Consequently, to control and predict the behavior of the cells to achieve better productivity and product yield, information concerning the cells physiological and metabolic states throughout the culture is necessary. Unfortunately, reliable and comprehensive process data from dynamic systems on living cells are not available for most cellular hosts including mammalian cells.[5] How-

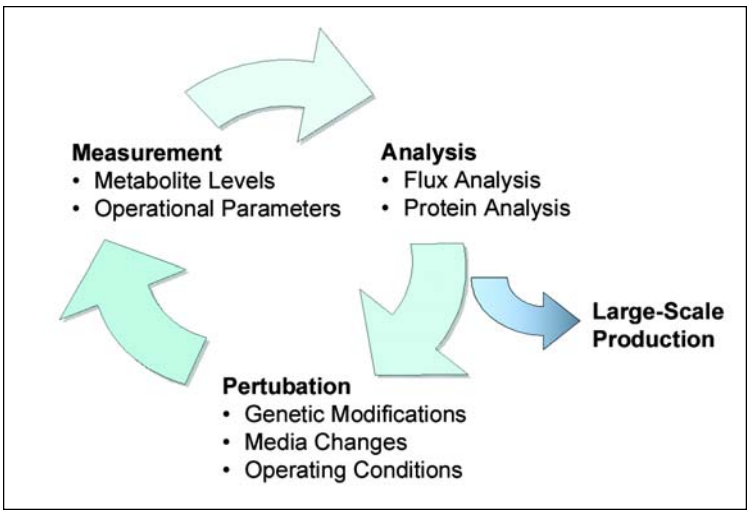

Figure 1. The iterative cycle of metabolic engineering.

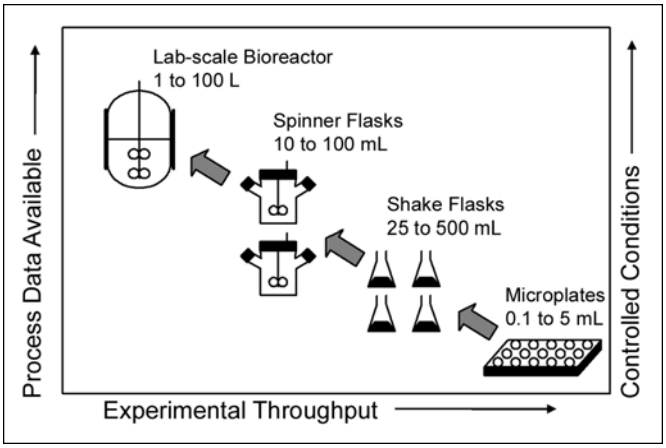

Figure 2. Illustration of the typical relationship between bioreactor monitoring capabilities and high-troughput experimentation.

ever, state-of-the-art non-invasive analytical technologies have been developed in the last few decades, which may help to provide the missing data, making it possible to model cellular processes and choose optimal cell culture operating conditions. This characterization of the bioprocess is typically performed during the development phase and tends to be a very lengthy affair, requiring important investment costs. A large set of experiments testing media components, cell lines, and environmental conditions must be assessed to determine optimal operation parameters in regard to productivity. Since so many conditions need to be evaluated, the commercial viability of using conventional bench-top bioreactors during the initial development is significantly reduced. For this reason, the industry is already looking to small-scale bioreactors that provide a well-defined environment and adequately monitor and control the culture, while providing accurate, complete, and useful data to reduce development process time. The range of data potentially acquired from small-scale bioreactors includes cell physiological and metabolic states as well as operational parameters. Furthermore, the small-scale bioreactor will significantly decrease development costs owing to its high-throughput qualities and the reduced use of raw materials, which are particularly expensive for mammalian cells. In the wake of Process Analytical Technology (PAT) tools, industry is now more then ready to utilize bioprocess data to model cellular performance to enhance bioproduction.

For accurate quantitative metabolic data, studies should be performed on intact living cells as opposed to *ex vivo* or *in vitro* experiments, such as metabolite extractions from cell sampling which exhibit low reproducibility in the literature.[5] Hence, Nuclear Magnetic Resonance (NMR) is one of the few technologies that permits the monitoring of metabolite concentrations and compartmentalization as well as intracellular pH *in vivo* in a non-destructive and non-invasive manner.[6] Combining the small-scale bioreactor with NMR has the added benefit of acquiring crucial metabolic data simultaneously without the necessity of sampling in a defined and controlled environment. Several small-scale bioreactors have been developed to be coupled with the NMR for *in vivo* measurements of yeast, plant, and animal cells. However, none of the configurations where designed for free suspension mammalian cells which, as stated above, are the most commonly used cellular host in the biopharmaceutical industry and are the main focus of this study.

Objectives

The primary objective of this project was to design a small-scale bioreactor perfusion system for mammalian cells free-suspension cultures. The design was adapted from a previously successfully developed bioreactor configured for plant cells in our laboratory.[7]

More specifically, the following conditions were analyzed:

- determine fluidization parameters allowing for adequate nutrient and oxygen mass transfer for maintaining high cell density culture
- characterize hydrodynamic profile of the bioreactor
- study and qualify mixing in the bioreactor
- demonstrate the bioreactor efficiency by performing on-line ^{31}P-NMR *in vivo* measurements

A Platform for Process Optimization

The production of a protein-of-interest depends on a combination of factors: genetic (e.g., expression levels of key enzymes), physiological (e.g., carbon fluxes, energetic state), and environmental (e.g., O_2, CO_2, temperature, and pH). Each of these conditions must be studied and monitored during cell cultivation for process optimization.[8] However, to date, most on-line monitoring tools only measure extracellular components, such as cell density and oxygen consumption to indirectly assess the physiological and metabolic state of the cells. Without intracellular measurements, available process variables are insufficient to fully characterize the process. Therefore, new on-line technology must be selected to acquire as much process data as possible, including both intracellular and extracellular measurements. More sophisticated models will then be developed to mathematically express the cellular activities with the intention of optimizing:

- cellular growth
- product yield
- growth medium composition
- operating parameters including pH, temperature, dissolved oxygen

In the past, cellular processes were lumped into a black box model, which were empirical by nature and gave no information of the underlying mechanisms of the cell metabolism. Metabolic engineering, on the other hand, is an evolved approach that has been refined to fill this gap by adequately measuring, analyzing, and designing bioprocesses optimally.[9,10]

Metabolic Engineering: A Useful Tool

Metabolic engineering adopts genetic engineering strategies such as recombinant DNA technology for strain improvement

by enhancing or creating new pathways by which to increase product yield. The main difference and advantage of this systematic approach is that it mirrors the age-old adage that "the whole is greater than the sum of its parts." In other words, while some cellular genetic strategies focus only on a particular pathway and a few of their key enzymes to increase product yield, metabolic engineering recognizes that the living cell is made up of thousands of complex and intertwined metabolic pathways that respond differently to changing environmental conditions. Therefore, a genetic change in one pathway may unknowingly have undesirable effects in others due to the interdependent nature of the metabolic network. Thus, it is insufficient to arbitrarily amplify specific enzymatic genes in a cellular host in the hopes of obtaining maximal protein production with no comprehension of the impact on the entire metabolic network. The amplification may have little or no effect on product yield; therefore, time and money would have been wasted in vain. Blind cellular mutations require long screening processes and give no understanding on the improvement itself. Consequently, the aim of metabolic engineering is to successfully direct metabolic flux toward valuable product formation by understanding the effects of genetic manipulations on the network or the "whole," making intelligent and directed genetic modifications.

In practical terms, metabolic engineering follows an iterative approach for the continuous improvement of the targeted phenotype based on a sequential series of experiments - *Figure 1*. The knowledge gained in each step leads to the next series of experiments. Where to start in the cycle depends on the objective of the process as well as the initial knowledge on the cells metabolic control. Often, a perturbation is first applied to the cellular host such as a genetic modification to impart improved qualities to the strain. Typically, several cultures will be conducted to obtain a metabolic characterization of the cells, including intracellular and extracellular metabolites levels, bioprocess conditions (pH, pO_2, and temperature), RNA expression, etc. Metabolic flux and flux control analysis will then give rise to models to better target the next modification. The more accurate and complete the data used to perform whole metabolic analysis, the less the number of iterative cycles will be necessary as desired results will be achieved faster reducing development time and cost. Once targeted results are confirmed by analysis, the bioprocess can be considered for large-scale production.

This data-driven approach can be used for many different applications for bioprocess optimization such as:

- improvement of production yield: directing carbon flow toward specific pathways or increasing enzyme activity
- recombinant protein production: cloning all necessary pathways into host to produce active molecule
- bioprospecting: identifying new cell-lines that exhibit therapeutic compounds or novel enzyme activity
- screening of drug candidates
- elimination or reduction of by-product formation
- strain improvement: more robust in terms of viability
- identifying pathways for cell line enhancement
- media design
- extension of substrate range: to use less costly raw materials or higher viability in previously toxic environment
- extension of cellular physiological conditions: increase tolerance to low oxygen concentration
- screening cell library for enhanced metabolite production

This list is far from exhaustive.[8,9] Any potential improvement to the strain and to environmental conditions, as well as novel discoveries can be verified and further enhanced with this approach making predictive changes a possibility. Up to now, metabolic engineering has been mostly employed to tailor specific traits of cellular hosts such as increased production of ethanol,[12] lactic acid,[13] lysine,[14] propane diol,[15] and therapeutic proteins.[16] All of these examples are industrially relevant processes and demonstrate the range of applicability of this approach. In more detail, Takiguchi and his colleagues[14] were able to increase lysine production molar yields from 7.5% to 30.6% by changing operational parameters based on molar flux distributions. These analyses were derived from metabolic reaction models developed with on-line measurements.

The shortcoming of metabolic engineering is that to use this approach efficiently and in a timely manner, specific tools must be on-hand. As defined earlier, this iterative approach requires many series of tests. Several cultivations are required under traditional methods to attain the large sets of data needed to properly characterize the metabolic network and identify control strategies. To significantly reduce costs, many researchers have begun to use small-scale bioreactors for this phase in the development process.[17,18,19] By using small-scale bioreactors that have high-throughput qualities, many metabolites may be monitored in parallel and the reduced volumes of the vessels save on expensive raw materials.

Small-Scale Bioreactors

To reduce material and labor costs and accelerate the development phase, the use of small-scale bioreactors is indispensable. In this body of work, a bioreactor is considered "small-scale" or "mini" if its volume is inferior to 100 mL with particular attention to culture tendencies in vessels below 10 mL, such as test-tubes and microtiter plates due to the ease of parallelization and automatization of these systems.[20]

It is important to recognize that regardless the volume of the bioreactor, it is essential that it provides a well-defined environment which can be monitored and controlled to obtain detailed strain characterization and process condition data. An advantage of using small-scale bioreactors is that they permit high-throughput approaches. However, in the past, the level and quality of monitoring and control of the cell culture was proportional to the bioreactor volume as seen in Figure 2. This trade-off was mostly due to the lack of appropriate analytical tools such as pH and dissolved oxygen probes whose relative size where not amenable for smaller vessels. However, the use of microtiter plates has become more interesting in the last several years due to the recent availability of innovative integrated miniature sensors helping to close the information

Nucleus	Isotopic Abundance	Biological Applications
^{3}H	0	Receptor-ligand interactions
^{1}H	0.9998	Metabolites, pH, redox
^{19}F	1.0	Cations, O_2, metabolites
^{31}P	1.0	Energy, cations, metabolites
^{7}Li	1.0	Transport
^{23}Na	1.0	Intracellular Na^+
^{13}C	0.011	Metabolites
^{2}H	1.5×10^{-4}	Membrane structure
^{17}O	3.7×10^{-4}	Water structure
^{15}N	3.7×10^{-2}	Metabolites
^{35}Cl	0.755	Intracellular Cl^-
^{14}N	0.996	Metabolites
^{39}K	0.931	Intracellular K^+
^{41}K	0.069	Intracellular K^+

Table A. NMR nuclei and their relative natural abundance and biological applications (adapted from Gillies et al., 1989).

gap between small-scale and lab-scale bioreactors.[21] There are still some limitations to the use of microtiters plates as bioreactors such as high evaporation rates and the relatively high risk of cross-contamination caused by aerosol formation.[20] Furthermore, the benefits of parallelization and automatization in a microtiter platform are counter-balanced by its inefficiency to precisely control operational parameters such as O_2 levels and to acquire *in vivo* metabolic data. Additionally, many believe that culture volumes are too small to adequately characterize the entire process and the cell line.[8,18] Therefore, other small-scale systems are developed and used to overcome these shortcomings.

While several miniaturized systems now exist on the market, it is difficult to find one that can fulfill monitoring and control requirements to simultaneously examine nutrient concentrations, metabolite levels, pH, oxygen, and temperature. The difficulty is not only in choosing the appropriate type of bioreactor for a specific bioprocess application, but combining the bioreactor with the proper analytical tools for extracellular and intracellular measurements and subsequent metabolic characterization.

Advantages of Non-Invasive Analytical Technology

Metabolic engineering approaches are highly dependent on the tools that are used to measure metabolite levels. Without analytical tools it would be very difficult if not impossible to verify or validate the perturbations or genetic changes applied to the cell line. Therefore, the accuracy of the models defined by metabolic analyses will be proportional to the level of sophistication of the analytical tools chosen. In other words, the choice of technology used to quantify metabolites will directly influence the quality of the results and determine the number of iterative cycles needed to obtain the targeted-outcome (i.e., increased production yield and cell robustness).

Two categories of analytical technologies can be distinguished: *in vitro* or invasive methods and *in-vivo* or non-invasive methods. Invasive methods require sampling for *in vitro* analysis by such instruments as HPLC,[22] MS,[23] spectrophotometer,[24] and nuclear magnetic resonance or NMR.[25] These analytical techniques will provide a global snap-shot of the metabolic state of the cell and will require several series of samples to readily follow metabolism as a function of time. There is some debate on the reliability of sampling methods since metabolites have proven to be unstable. Several studies have shown that inconsistencies in the literature concerning metabolite levels are due to sampling and that these methods may not adequately represent the true metabolic state of the cells.[5,26]

On the other hand, non-intrusive methods allow for on-line *in vivo* measurements of metabolites over time and other important cell culture parameters such as pH, dissolved oxygen, and temperature, while eliminating the necessity of sampling and reducing contamination risks. IR, Raman, fluorescence, confocal optical imagery,[6] and NMR spectroscopy[27] are all examples of this category. NMR is unique as it can distinguish metabolite concentrations as a function of space (i.e., between intracellular and extracellular space) and measure compartmentalization in the cell providing key parameters for subsequent process modeling.[28]

NMR Spectroscopy of Living Cells

Physicists developed NMR spectroscopy in the 1940s, but it was only in the early 1970s that it was used for the first time for *in vivo* measurements of intact red blood cell suspensions albeit in non-viable conditions.[29] Since then, multiple applications in the biotechnology field have been reported and continue to grow.[30,31] The popularity of this instrument is owing to its non-invasive and non-destructive nature as well as its capacity to measure metabolite levels in complex mixtures without the need for specific assays. The metabolic data elucidated from NMR spectra is used to observe and measure intracellular pH, flux analysis, metabolite quantification, and biochemical kinetic reactions[32] and is of great importance for such disciplines as metabolic engineering.

The basic principle of NMR spectroscopy is that certain nuclei possess intrinsic magnetic moments which are sensitive to magnetic fields. When these nuclei are submitted to strong magnetic fields, their magnetic moments align themselves either parallel or antiparallel to the field, creating a net magnetization. The difference in energy, "E," of the state or the direction of the magnetic moment of each nucleus depends on the strength of the applied magnetic field and the gyromagnetic ratio of the particular nucleus. Resonance is produced when transition between the two energy states occurs due to the application of bursts or pulses of electromagnetic energy at a specific radiofrequency during the NMR experiment. The measured resonance signal is specific to the nucleus and its environmental conditions (i.e., the position of nuclei in a molecule or the solution pH) as well as being proportional to the number of nuclei present. Therefore, NMR also can be used as a quantification tool.[32] The various

nuclei used in NMR are listed in Table A with their respective relative natural abundance and biological applications.

While there are several different nuclei to choose from when using *in vivo* NMR, one of the most commonly studied is ^{31}P due to its high natural abundance and the importance of phosphorus in essential metabolic compounds such as nucleosides phosphates (ATP, ADP, AMP, NADPH), sugar phosphates (glucose-6P and fructose-6P) and inorganic phosphate (Pi).[32] The majority of metabolic pathways employ ATP and this molecule plays an important role in metabolic reactions and control. Furthermore, ATP levels are considered to characterize the energetic state of the cell. Intracellular flux analysis performed by Henry et al,[34] correlated ATP levels to cell productivity demonstrating the relevance of following the phosphate isotope using NMR spectra. Additionally, ^{31}P-NMR allows for the monitoring of intracellular pH due to the sensitivity of the chemical shift of the inorganic phosphates to pH intermolecular effects.[28]

Though *in vivo* NMR is a powerful analytical tool providing on-line environmental and metabolic measurements of the cell culture, this technique has a few limitations. The most important is its lack of sensitivity. For a metabolite to be properly identified using NMR, its total concentration in the cell culture must be above 0.1 mM. However, many critical metabolites are only found in low concentrations (less then 0.1 mM) in the cell. The most common way to circumvent this problem is by increasing cell density until high quality spectra are achieved. Typically, NMR studies of suspended cells call for cell densities of approximately 10^7-10^{11} cells mL^{-1}, depending on cell type and size.[32] Therefore, certain process or operation requirements must be met allowing for a viable high density cell culture:[29]

1. Cell suspension must be homogeneous and within the NMR reading zone.
2. Cell suspension must be adequately perfused for proper nutrient delivery and waste removal.
3. Cell suspension must be adequately oxygenated.

To meet all of these constraints, the small-scale bioreactor is an invaluable tool.

Small-Scale Bioreactor Combined with NMR

High cell density increases sensitivity and permits shorter acquisition times for NMR spectra, providing real-time monitoring. However, this condition also will necessitate a higher degree of control to provide adequate nutrient levels, oxygen supply, waste removal, and other environmental parameters. Therefore, this control can be provided by small-scale bioreactors housed in a standard NMR tube (10-20 mm

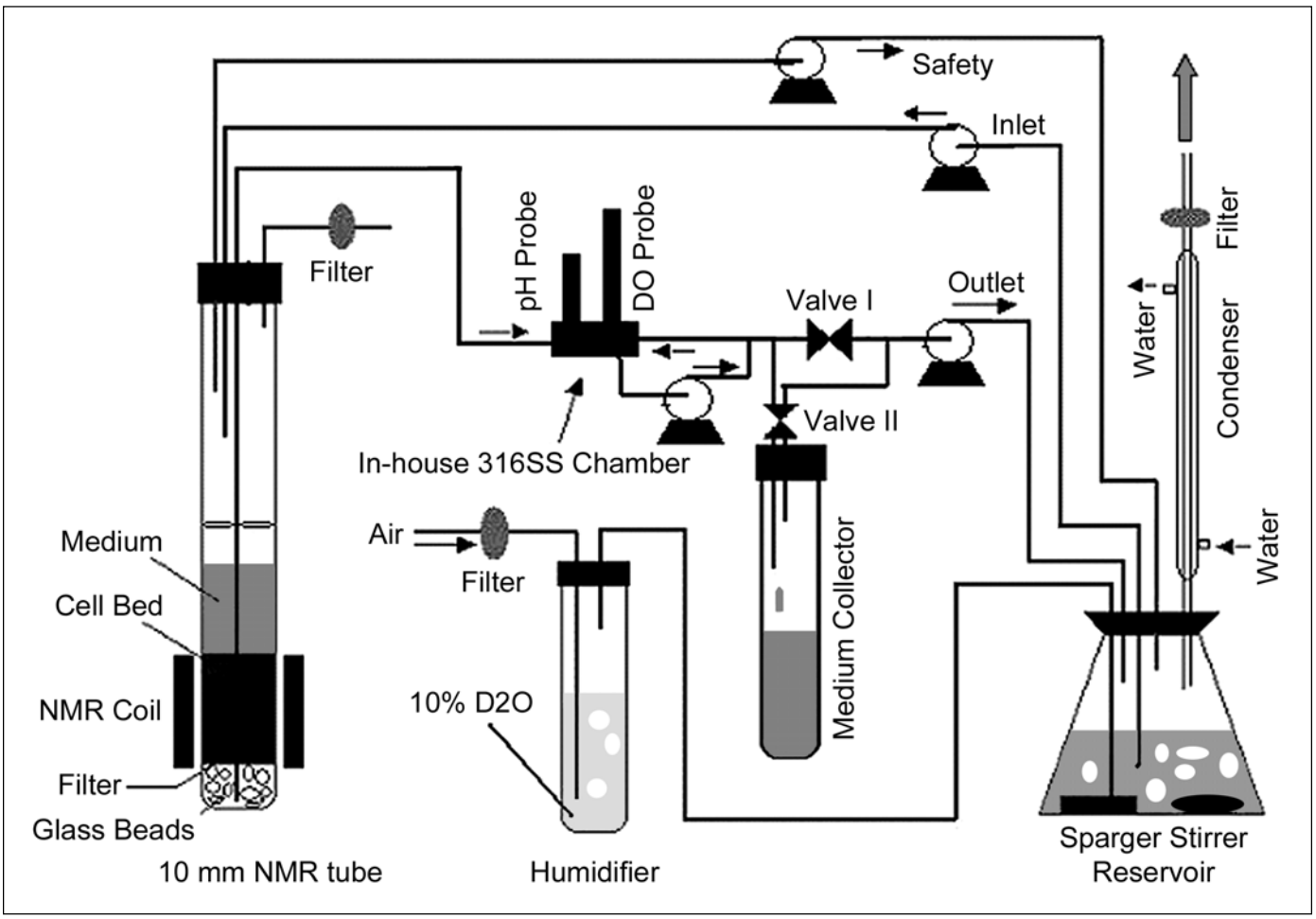

Figure 3. Small-scale bioreactor platform for plant cells.

diameter, 3-20 mL culture volume). Many configurations have been designed and tested using several types of cells, including airlift, microcarrier, hollow-fiber, and compact bed bioreactors.

The airlift small-scale bioreactor has the advantage of being relatively simple and has been used to study bacteria and yeast.[35,36] Oxygenation is provided by bubbling gas in the central tube of the bioreactor as is done in conventional sized air-lift vessels. However, the presence of bubbles in the NMR detection region can disrupt the homogeneity of the magnetic field and broaden the resonance. To perform long-term studies, this configuration is not adequate since it does not bestow suitable conditions for waste removal (i.e., lactate and CO_2) over time.

Perfusion systems for the small-scale bioreactor platform have the advantage of providing constant nutrient and oxygen supply, while simultaneously removing waste products which allows for long lasting high cell density cultures.[37] However, sophisticated techniques need to be adopted to maintain the cell culture in the NMR reading zone. Many have chosen to make use of microcarrier beads to immobilize the cells in the bioreactor and prevent cell wash-out. For example, Shankland and colleagues[38] immobilized A549 mammalian cells to macroporous gelatine carriers in a perfusion reactor for ^{31}P and ^{13}C NMR study. Another configuration for anchorage-dependent cells is the Hollow-Fiber System (HFBR). Gillies et al,[39] have worked extensively with the HFBR since up to 70% of the reactor volume can be occupied by the cells with this technology and cell densities have been reported to reach above 10^8 cells mL^{-1}. These conditions provide ideal circumstances for NMR spectroscopy as seen by real-time ^{31}P NMR studies (180s acquisition time) of hybridomas, CHO cells as well as C-6 rat glioma. However, adherent cells are not as commonly used in industrial bioprocesses, due to the difficulty of maximizing surface to volume ratio in large-scale bioreactors and cell transfer through the bioreactor chain. Therefore, there is concern that metabolic data obtained from adherent cells may not be representative of the true nature of free-suspension cell cultures. Consequently, research groups are designing small-scale bioreactors that better reflect their large-scale counterparts such as Gmati et al.[7]

The long-term *in vivo* NMR study of high density plant cell cultures was successfully accomplished by our laboratory by developing a small-scale perfusion bioreactor that sequestered the plant cells in a packed-bed, while providing a homogeneous external environment - *Figure 3*.[7,40] Significant characterization of the hydrodynamic and mass transfer profiles of the bioreactor demonstrated a perfectly mixed system as well as providing control of the perfusion parameters such as oxygen and nutrient supply, pH, and temperature. Inspired by this body of work, a small-scale perfusion bioreactor for free-suspension mammalian cells is developed.

Design Constraints for Free-Suspension Mammalian Cells

To our knowledge, no other configuration has been successfully designed for *in vivo* NMR measurement of free-suspension mammalian cells. This is invariably due to the specific design constraints imposed by the necessity for high cell density sequestered in the NMR reading zone. Therefore, oxygen becomes a limiting factor in the system. Low solubility of oxygen in media entails that gas diffusion only will not adequately provide for the metabolic needs of the cell. Furthermore, mammalian cells negatively react to high oxygen concentrations and it is generally recommended that pO_2 is maintained between 25 to 50%.[41] Increasing perfusion rate is the simplest solution to assure that oxygen consumption rate of the cells is satisfied. However, increasing flow rate to

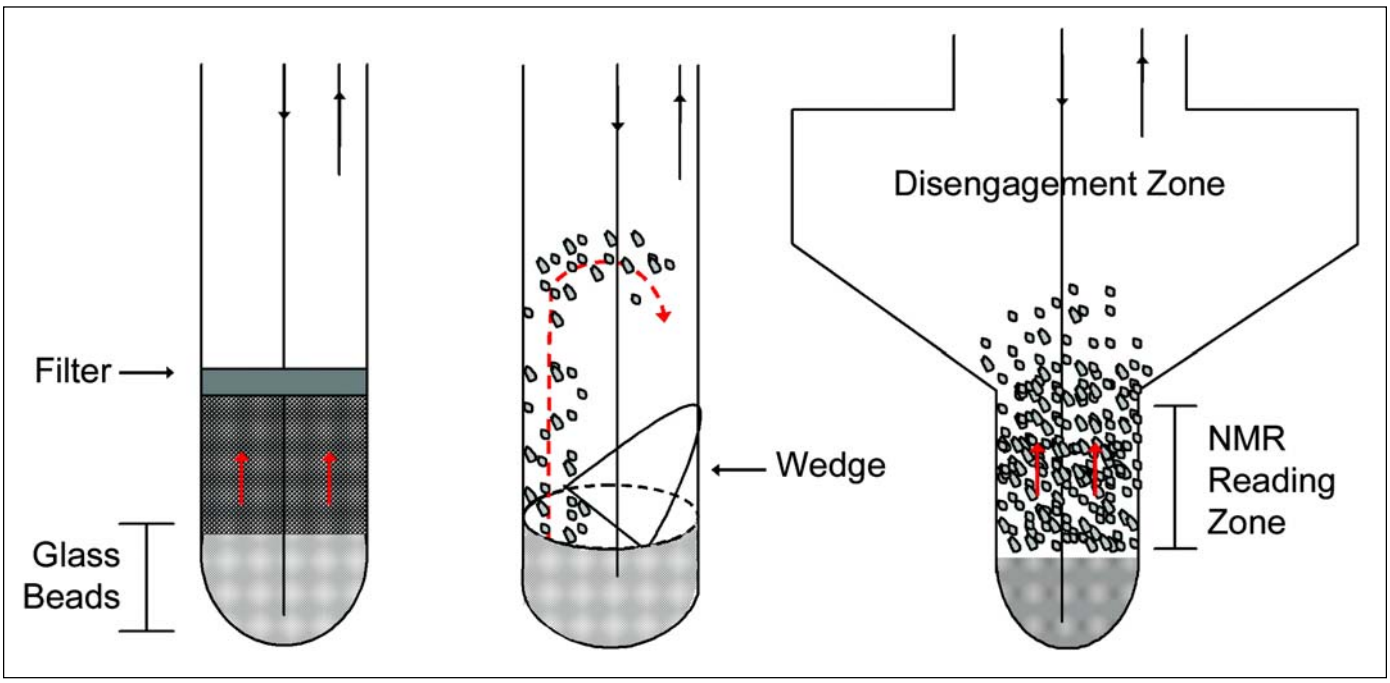

Figure 4. Potential small-scale bioreactor configurations for free-suspension mammalian cells in a 10 mm diameter NMR tube.

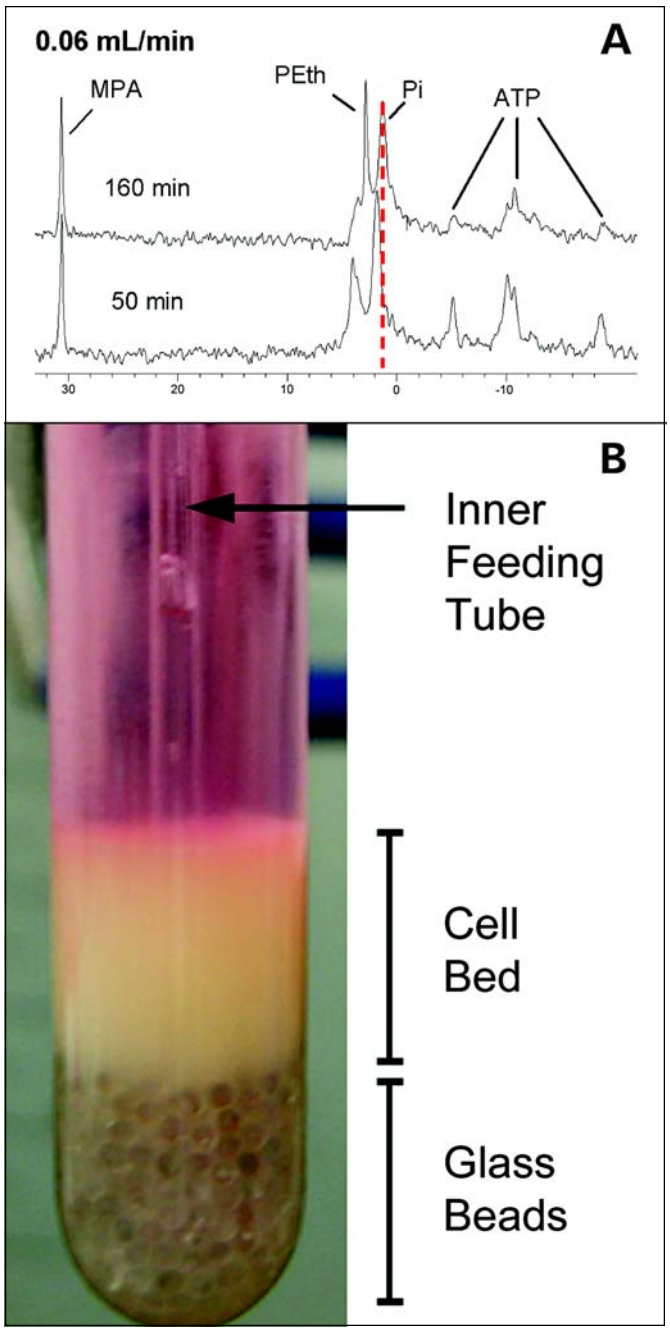

Figure 5. A. Proton-decoupled ^{31}P NMR spectrum of in vivo analysis of 3-d-old CHO (Chinese hamster ovary) cells perfused at 0.06 mL min^{-1}. B. Perfused CHO cell bed (1.44 x 10^8 cells) at 0.06 mL min^{-1} in small-scale bioreactor.

suitable levels will most definitely cause cell wash-out from the bioreactor, due to low cell density. The majority of the work for this study will require determining and constructing the appropriate configuration that will allow for high flow rates, while maintaining free-suspension mammalian cells in the NMR reading zone.

Figure 4 presents the various small-scale bioreactor configurations studied. All of these designs have the potential to fulfill the elementary requirements for *in vivo* NMR measurements. The packed-bed configuration (A) has the advantage of being relatively simple to construct and could satisfy requirements for high flow rate and sequestered cells. But mammalian cells are fairly sensitive to shear stress and the packed-bed may create unviable conditions for the cells. For example, the lack of cell walls and the plasticity of the cell membranes may foster a very tight compact bed which could produce preferential media currents in the bed and heterogeneous conditions. On the other hand, the whirling motion bed (B), initially developed for drying applications,[42] should be compatible with the small-scale bioreactor, because the circulating motion allows for better mixing as well as higher flow rates, while maintaining the cells in the NMR reading zone. The purpose of the wedge is to disrupt the flow and create a preferential current which is the driving force of the whirling motion. The superficial velocity of the fluid will decrease as it goes up the wedge directing the cells back to the bottom of the tube where they will be carried upward again by the entering media. The whirling motion provides an effective method to properly oxygenate the cells, but may be difficult to apply. Optimal wedge configurations and flow rates will have to be evaluated to assure satisfactory operating conditions. Another promising design is the fluidized-bed with the disengagement zone (C). The top section of the fluidized bed is expanded to abruptly reduce the superficial velocity of the media below the minimum fluidization velocity, which serves to return the cells to the narrow part of the NMR tube preventing cell wash-out and assuring high cell density. The advantage of the disengagement zone is that it allows for higher flow rates of the fluidized liquid, which supplies additional oxygen levels to the cells. However, this configuration requires a custom designed NMR tube and probe. Nevertheless, all of the presented configurations merit further investigation to determine the most efficient design.

As stated above, there is one significant limiting factor of the design: oxygen availability. The ability to satisfy mammalian cell respiration is at the base of the successful design and operation of the small-scale bioreactor. Consequently, one of the first steps is to identify the minimal perfusion flow rate required for sufficient oxygen delivery and to subsequently monitor the dissolved oxygen concentration throughout the cultivation. Using a lab-built respirometer, the oxygen specific uptake rate, qO_2, can be calculated by plotting a time profile of dissolved oxygen and the oxygen consumption of the cells in culture.[44] The qO_2 is then used to determine minimal perfusion flow rate (Q) for a given cell density (n) and dissolved oxygen concentration (DO) using the following relation:

$$Q = \frac{qO_2 \cdot n}{DO}$$

This estimate provides a crucial starting point for the fluidization assays to follow regardless of the small-scale configuration studied.

Mixing of the cells also requires specific attention owing to the fact that it will ensure cell suspension and provide homogeneous nutrient and oxygen concentrations. To characterize the quality of the mixing, Residence Time Distribu-

tion (RTD) experiments will be performed by measuring the evolution of a saline pulse with an electrical conductivity detector. The tracer concentration will then be evaluated in terms of the dimensionless Péclet (Pe) number.[45] When Pe is close to zero, axial dispersion is large and when Pe tends to infinity, axial dispersion is low. By uncovering and comparing the specific mixing dynamics of each small-scale bioreactor, the most appropriate configuration can be chosen for the design constraints imposed by *in vivo* NMR measurements.

Once fluidization and operational parameters have been discerned, *in vivo* NMR measurements of free suspension mammalian cells can start. The spectra will give additional information concerning cell viability, appropriate cell density, and/or dissolved oxygen concentration and further improvements can be applied to the small-scale bioreactor platform to achieve long-term monitoring and control of the cell culture. Preliminary NMR studies of the packed bed design demonstrate that *in vivo* measurements of free-suspension mammalian cells are possible. However, as speculated, the viability of the cells decreases as a function of time and does not allow for long-term *in vivo* measurements as seen in Figure 5 by the chemical shift of the inorganic phosphate (Pi) peak. A chemical shift to the left is indicative of an imposed stress to the cells such as a lack of oxygen. Additionally, the peak intensities decrease as a function of time demonstrating cell death. The packed bed appears to create preferential currents which will be verified by RTD. The other bioreactor configurations will be tested in the meantime and evaluated on the quality of the spectra as well.

Conclusion

Enhancing cell lines, media, and bioprocesses for greater bioactive protein delivery and cell robustness is the aim of all biopharmaceutical manufacturing industries. To fulfill this goal in an efficient and timely manner, metabolic engineering is progressively becoming an invaluable tool. This approach will lead research and development to better control strategies by targeting the right genes, pathways, and proteins for bioprocess expansion. The small-scale bioreactor combined with NMR technology for *in vivo* measurement provides accurate, relevant, and real-time physiological, operational, and metabolic data necessary for comprehensive metabolic analysis. The development of this bioreactor platform for free-suspension mammalian cells is critical owing to the importance of this particular cellular host in the industry. Preliminary tests have shown that the packed-bed configuration enables *in vivo* NMR measurements for CHO cells. However, optimal operating conditions and bioreactor design still need to be determined. The whirling-motion bed offers particular promise in satisfying all design constraints, providing necessary metabolic data for process optimization. Regardless of the final configuration, the small-scale bioreactor will be able to host numerous types of suspension cells as well as adherent cells and make full use of long-term *in vivo* NMR measurements.

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A well-known and accomplished vaccine research leader discusses the state of vaccine research today, the challenges ahead, and how Wyeth continues to play a significant role in vaccine research and development.

PHARMACEUTICAL ENGINEERING Interviews

Dr. Emilio Emini, Executive Vice President of Vaccine Research and Development, Wyeth Pharmaceuticals

by Cathy Middelberg, Member, *ISPE Pharmaceutical Engineering Committee*

A well-known and accomplished vaccine research leader, Emilio Emini led high-quality research organizations at Merck Research Laboratories and at the International AIDS Vaccine Research Initiative before joining Wyeth in 2005. Dr. Emini began his career in 1980 with a doctorate from Cornell University Graduate School of Medical Sciences in the fields of microbiology (virology), genetics, and biochemistry (molecular biology). He was a Postdoctoral Fellow in the Department of Microbiology at the State University of New York at Stony Brook from 1980 to 1983. In 1986, Dr. Emini turned his full-time attention to the study of the immunobiology and genetics of the Human Immunodeficiency Virus (HIV). He led the Merck biology programs that yielded the discovery of indinavir and efavirenz, two of the first potent anti-HIV chemotherapeutic agents. Dr. Emini was the founding Executive Director of Merck's Department of Antiviral Research, and in 1997, became the Vice President of Merck's Vaccine and Biologics Research. In 2004, Dr. Emini served as Senior Vice President and Head of Vaccine Development at the non-profit International AIDS Vaccine Initiative, where he helped establish clinical and laboratory infrastructure in African countries to support the study of experimental AIDS vaccines, as well as guide the early development studies of several AIDS vaccine approaches. In November 2005, Dr. Emini returned to the pharmaceutical industry as Executive Vice President of Vaccine Research and Development at Wyeth Pharmaceuticals, where he is focused on the design and development of novel vaccines for bacterial and viral infections. Dr. Emini is a Fellow of the American Academy of Microbiology.

Q How did you become interested in vaccines and vaccine Research and Development?

A If you look at the history of vaccination over the last 100 years, it is fair to say that no other intervention, other than a readily available supply of clean water, has had such a profound effect on human health. Many of the 25 years that I have spent in pharmaceutical research have been focused on vaccine R&D. While at the Merck Research Laboratories, I was privileged to work on vaccines for recently licensed products for prevention of rotavirus infections, the cause of severe, dehydrating diarrhea in infants and young children, and for prevention of papilloma virus infections, the cause of cervical cancer. In late 2005, I joined Wyeth Pharmaceuticals as the head of Vaccine Research and Development, after spending about two years at a non-profit organization focused on HIV vaccine research.

"If you look at the history of vaccination over the last 100 years, it is fair to say that no other intervention, other than a readily available supply of clean water, has had such a profound effect on human health."

Q Why Wyeth?

A I came to Wyeth because of my continuing interest in vaccine Research and Development. What I saw was a commitment and dedication to the development of novel vaccines against important infectious and non-infectious diseases.

Not only is Wyeth's vaccine future of interest personally, but Wyeth has had a long and significant history in vaccine Research and Development. This history included the production of the small pox vaccine that played a substantial role in the worldwide eradication of this disease. Wyeth also manufactured the oral polio vaccine, which was used to successfully eliminate poliomyelitis in North America.

Q Can you give me specific examples of future Wyeth vaccines?

A As you know, the very successful vaccine Prevnar™, was developed at Wyeth for the prevention of pneumococcal disease in infants. Pneumococcal infections can occur in the lungs, the bloodstream, and the covering of the brain. Currently, Wyeth is in the process of developing a second generation of this vaccine that will provide an even broader protection against multiple serotypes of the pneumococcus organism. This second generation vaccine will have an even greater impact on the health of the human population than the extraordinary impact already demonstrated by the current vaccine. The development of this second generation vaccine is intellectually and technically challenging, and when successful, will represent the most complex biological product ever produced.

Other research programs at Wyeth include the development of a vaccine for the prevention of meningococcal type B infections, as well as a vaccine that could help prevent the progression of Alzheimer's disease.

Q Given the success of vaccines and anti-infection agents in controlling disease, what do you perceive as the major public health challenges that the world faces?

A Unfortunately, in spite of the significant impact vaccines have had over the past century, we are far from eradicating the scourges of infectious diseases in the human population. We have the issues of newly emerging infectious disease, the best example being HIV AIDS that first made its worldwide appearance in the late 1970s. This is a disease that is responsible for more deaths than any other infectious

A History of Vaccines

Historical records show that inducing the development of immunity to disease by providing the immune system with harmless microorganisms was practiced by the Chinese as early as the 10th century. This was done through the process of introducing a small amount of smallpox virus by inhalation through the nose or by making a number of small pricks through the skin (variolation) to create resistance to the disease. Unfortunately, this practice often resulted in serious disease.

In 1796, British physician Edward Jenner realized that milkmaids who had contracted cowpox – a mild illness resulting from the practice of milking – appeared to be immune to smallpox. Jenner ultimately showed that purposefully inoculating healthy people with infectious cowpox material could in fact prevent the development of smallpox. The practice became known as "vaccination." The word is derived from *vacca,* the Latin word for cow.

The following centuries saw the creation of vaccines for other diseases. In 1885, French scientist Louis Pasteur developed the first vaccine to protect humans against rabies, and in 1897, a vaccine against typhoid fever was developed in England.

Vaccines have since been developed for many other infectious diseases, including anthrax, cholera, diphtheria, Haemophilus influenzae type b (Hib), hepatitis A, hepatitis B, human papillomavirus, influenza, measles, mumps, meningococcal disease, pertussis (whooping cough), plague, pneumococcal disease, polio, rotavirus, rubella, tetanus, tuberculosis, varicella (chickenpox), and yellow fever.

Currently, immunization saves the lives of two to three million children every year. However, there is still much work to be done, both in the delivery of existing vaccines and in the development of new vaccines. Of the 10.5 million child deaths that occur annually, 2.5 million are due to diseases that are preventable by vaccines.

Today, malaria, adult tuberculosis, and HIV are major targets of vaccine development, as are the tropical diseases such as hookworm, onchocerciasis, schistosomiasis, amebiasis, Chagas' disease, leishmaniasis, Buruli ulcer, Chlamydia, leprosy, leptospirosis, treponematoses, dengue, and Japanese encephalitis.

Content for this history is compiled from information provided by the World Health Organization, Centers for Disease Control and Prevention and the Global Alliance for Vaccines and Immunization (GAVI).

disease today. And yet, this is a disease for which a vaccine is not available. Considerably more work needs to be done to understand the basic nature of this infection. On the other hand, we also have infectious diseases that have been with humans throughout history for which we have been unable to develop vaccines. The best example of this is malaria. And finally, there are diseases for which vaccines have been around for many years, but are still responsible for considerable disease and death in the developing world countries. An example of this is measles.

Q So what are the challenges that researchers face in vaccine development to address these issues?

A We are challenged to understand the mechanisms of these diseases, which will require basic and focused scientific research. This is certainly the case for HIV and malaria. There are also social and political challenges. For example, the lack of effective healthcare delivery structures in some parts of the world prevents the delivery of some important and effective vaccines to vulnerable populations.

Q Do you see any hope that we can overcome these challenges?

A I have considerable hope that the scientific challenges will be overcome. The history of science teaches us that perseverance, technological improvements, and the human capacity for insight will provide the answers to today's questions. I also have a lot of hope that the social and political issues that often stand in the way of providing effective vaccines also will be overcome. Over the past decade, we have already seen a number of examples of public and private organizations providing the finances and infrastructure for delivering vaccines to the developing world. These organizations are cooperative endeavors of governments, private foundations, and companies working together for the common good.

Q What can be done to accelerate research and development of vaccines for diseases such as HIV and malaria?

A To accelerate research and development, we need to continue to foster and expand the existing collaborative research efforts of private industry scientists, academic scientists, and government researchers. Each of us brings unique capability and perspective to the research questions. It is only by continuing to work collaboratively that we can hope to arrive at the needed answers.

Q How will vaccines of the future affect the practice of medicine?

A The prevention of disease is always preferable to having to treat the disease.

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Global Tracking System: Case Study in Risk-Based Validation

by Philip Rees, Marcel Boere, Frans van Oosten, and Giorgio Civaroli

This article discusses how the risk assessment method was applied to the validation effort of a pilot global tracking system.

Introduction

Astellas Pharma Europe Ltd, on behalf of Astellas Pharma Inc., has implemented a global pilot of a Corrective and Preventative Action (CAPA) and Tracking System to support quality management processes. The rollout program is extending usage of the system to all Astellas sites across the world.

Application of the risk assessment method ensured that the validation effort was properly focused on the areas of the system that were important from a regulatory perspective, and contributed significantly to the widespread acceptance of the new system.

Scope

The system uses a proprietary software application for tracking CAPA and process deviations and defines a number of business workflows for analysis of GMP critical processes with electronic signatures. The software is GAMP Category 4 and the validation strategy is based on implementation of current industry standard risk assessment methods.

The global pilot was designed to replace a series of paper-based systems and methods used throughout the Astellas Pharma Group in the management and tracking of QA business processes (change control documentation, complaints, deviations, and CAPA). This involves all areas of manufacturing, sales, and distribution. The new system includes use of electronic signatures at key points in the business workflows, employing digital technology to guarantee record authenticity, integrity, and confidentiality.

The manufacturing sites use all of the core workflows, whereas distribution sites use only those which apply to them. The global pilot was

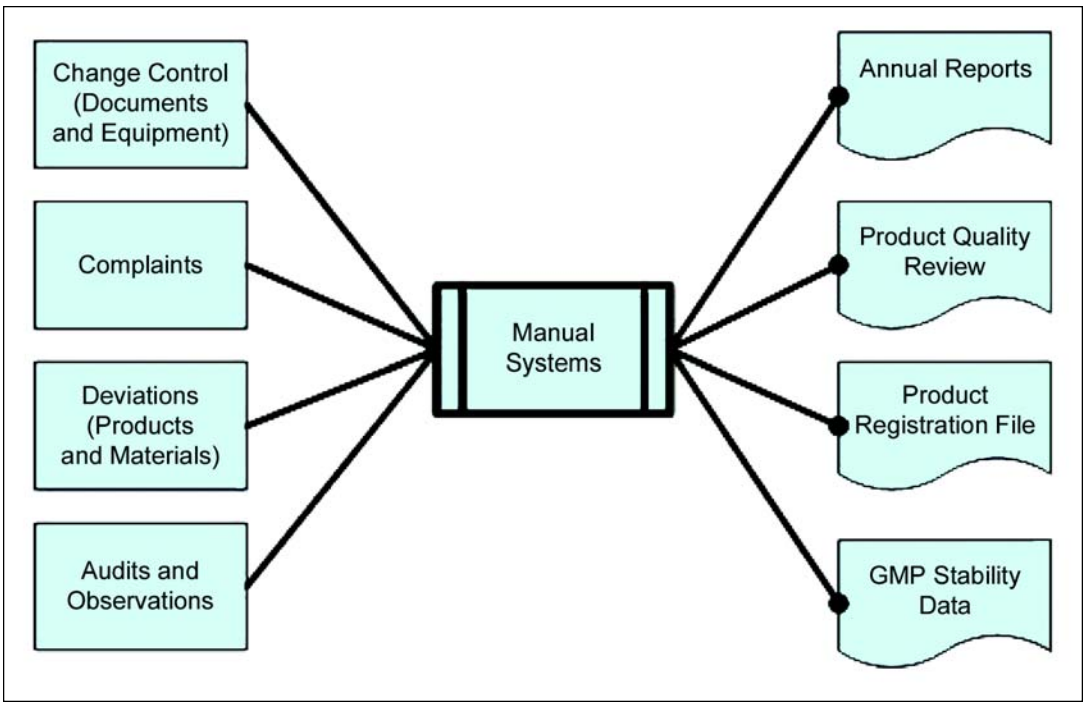

Figure 1. Overview of previous systems.

completed in nine months with improved efficiency and built-in compliance deriving from the risk assessment method.

Implementation

Correct handling of QA business processes requires a formal tracking procedure. By tracking process deviations, people involved can tell what stage the process is in at any given moment, how much work has been done, and what still remains to be done. The workflow management system is designed to provide this functionality.

Within Astellas, all GMP required data is collected under responsibility of the Quality Management (QM) Department. It was previously managed using several individual systems, which were not linked to one another. To document process deviations and track their follow-up, this information had to be combined and interpreted manually. These manual systems and their interpretation were not generally available to QM Departments worldwide. Additionally, management reporting within QA for the monitoring of day-to-day operations required costly manual labor.

The situation needed improvement to reduce the amount of work for GMP compliance and to produce the "Product Quality Review" required by GMP on time with accurate data. The chosen software package was able to integrate required functionality and supply the reports that were needed.

The QM Department identified the need for such a global system and was the sponsor for this project.

Project Objectives

The objective of the project was to develop and implement a software application to automate existing work methods in QA. All manual systems would be phased out after successful implementation of the new application. Disruptions to normal working practices would need to be minimized by maintaining current working processes as much as possible - *Figure 1*.

In the new situation, all process deviations are to be kept in one integrated CAPA and Tracking System. This system provides registration, workflow management, reporting facilities, and the functionality required to support QA management.

Starting Assumptions

To achieve project objectives, the following assumptions were made:

- Current working procedures will serve as the basis to move from existing manual systems to software driven workflows with minimal redesign.
- Where necessary, local processes will be adapted to the new business model.
- Each site will create and validate local workflows during the PQ phase, which will then be used in their production and QA environments.

Selection of Application

When selecting the software application, the following criteria were applied:

- The application must be a commercial software package.
- The package should be compatible with the functionality described in the core URS.
- The package must be capable of running GMP processes and FDA 21 CFR Part 11.
- The package must be widely used in the pharmaceutical industry.
- The package must use a database that is familiar to Astellas technical staff. This condition is necessary to ensure smooth transition to the implementation phase.

Benefits

The following benefits were identified for the project.

Tangible Benefits

- avoidance of additional headcount by automating the yearly Product Quality Review
- increased productivity through global information supply
- quality improvement which leads to less rework and rejections, which reduces costs to the business

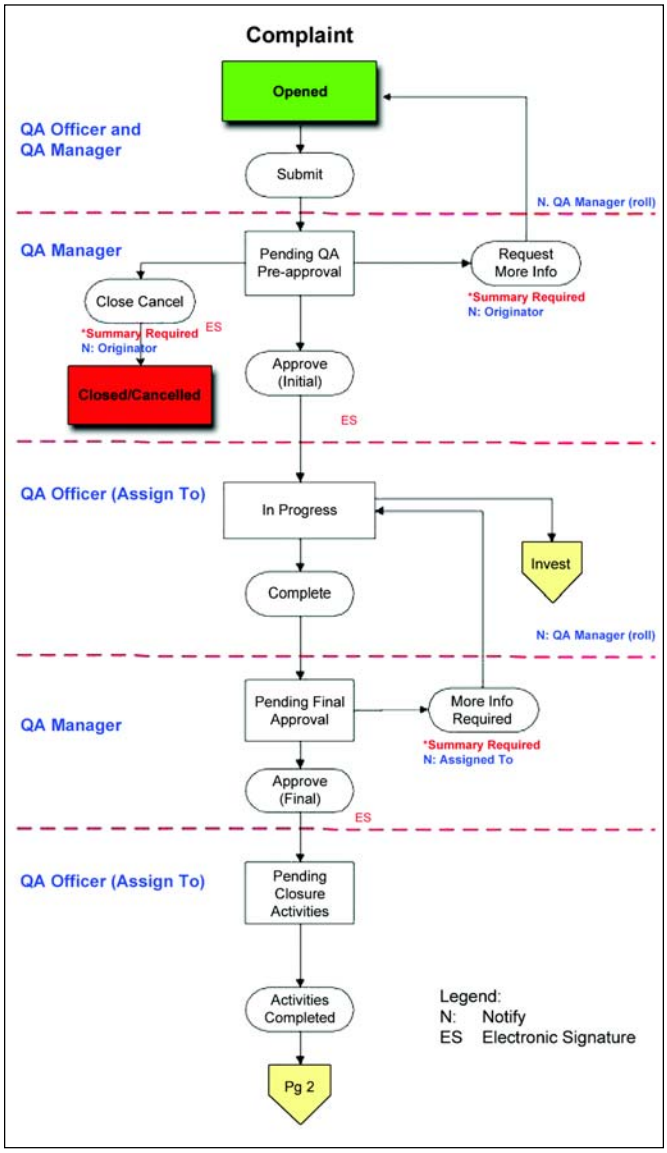

Figure 2. Sample workflow.

Available Workflows	Distribution Sites	Manufacturing Sites
Customer Complaints	X	X
Incidents	X	X
Investigations	X	X
Audits	X	X
Observations	X	X
CAPA	X	X
Effectiveness Checks	X	X
Tasks	X	X
Legal Claims	X	X
Refunds	X	X
OOS in Laboratories		X
Change Control		X
Supplier Complaints		X
Product Deviations		X

Table A. Workflow summary.

- no effort needed to make the existing systems compliant with 21 CFR Part 11, because they will be replaced

Intangible Benefits

- possibility of Periodic Product Review and trend analysis
- accessible and complete overview of QA processes in a single system
- shorter lead-times in investigations to allow faster corrective and preventive actions
- improvement of customer satisfaction through faster response and better information
- faster and more accurate investigational reports with consolidated data on improvements within and across workflows

Workflows

The software application is configurable as it is used for managing various types of deviation workflow. The possible states of a deviation are pre-determined and correspond to the various stages in the management lifecycle of the deviation.

The standard workflows implemented in the global pilot were as follows. These are available in the central application server and can be used by any site in the group. Supplementary workflows can be added locally by each site as required. The last four workflows were developed specifically for pharmaceutical manufacturing sites - *Table A*.

Sample Workflow – Incident Management

A typical workflow defined within the application is as follows - *Figure 2*.

System Architecture

The system architecture is based on a global client-server model, such that all sites use the same central server and can link both to this database and their ERP system - *Figure 3*.

Each client can access the application using a standard internet interface, which eases global rollout and training.

Data Interface

The data interface between the ERP systems used by the manufacturing sites and the central application server was specifically developed for this project. Data exchange takes place according to a predefined schedule via an intermediate database, which has been validated and is maintained under change control. In this way, updated information on materials and lots is available within the application.

In the next phase of the project (currently planned), data exchange will be extended to include laboratory information systems - *Figure 4*.

Validation Strategy

The validation strategy is in line with industry standard methodology with extensive use of the risk assessment method according to the narrow interpretation of 21 CFR Part 11. The strategy was oriented toward ensuring compliance with predicated GMP rules and business requirements, focusing on identification of system functions which may affect product quality, product safety, and record integrity. Where risks were identified, mitigation actions were implemented and

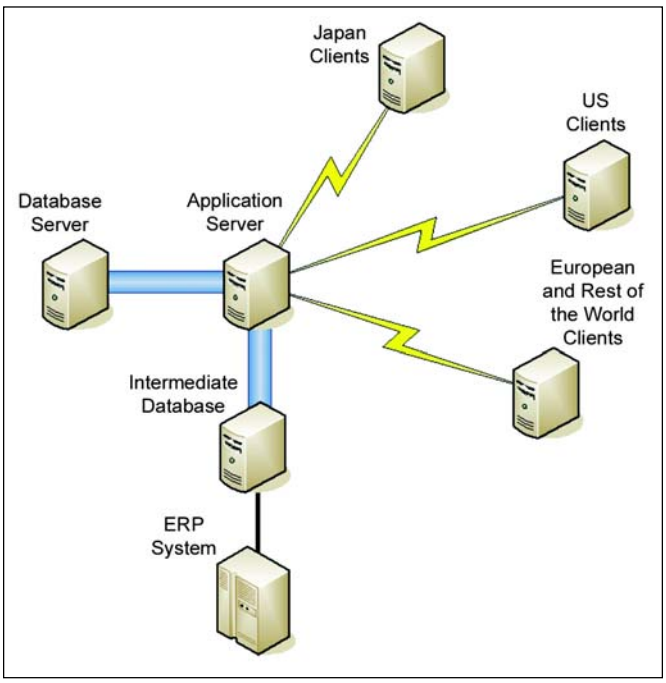

Figure 3. Global architecture.

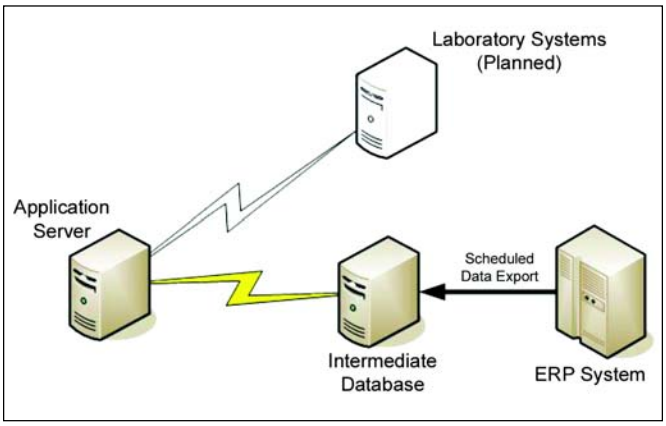

Figure 4. Corporate data exchange.

followed up in order to reduce such risks to an acceptable level.

The software system was delivered with an existing set of Installation Qualification (IQ) and Operational Qualification (OQ) documentation from the supplier, called IQ1 and OQ1. As a result of the risk assessment, a number of supplementary tests were identified and added to focus on GMP functions. This additional activity is referred to as IQ2 and OQ2.

The validation relationships can be represented as follows - *Figure 5*.

The IQ and OQ performed by the supplier were accepted as reference documents because of the successful Vendor Audit.

- Supplier activities were done in a separate environment.
- Activities performed by Astellas were in a company-controlled environment called 'QAS' which was equivalent to production.
- The PQ was performed by each site using real workflows in conformance with defined user needs and intended uses. These were transferred to the production environment after completion of PQ.

The validation of the central instance is the principal reference for additional validation work required in rollout to the other sites. Since all sites use the same central system, this is subject to IQ and OQ, whereas the workflows implemented at each site are subject to PQ. Sites may reuse workflows developed at other sites with significant cost reduction and economies of scale.

Environment Management

Multiple server environments were used to manage configuration, validation, and change control. The QAS and production environments were qualified as part of the project and remain available to sites who need to continue development of new workflows.

Figure 6 shows the environment architecture and migration flows.

Vendor Audit

As required by the company's corporate policy, a supplier audit was performed in which the supplier's quality system and validation package were reviewed in detail. This activity

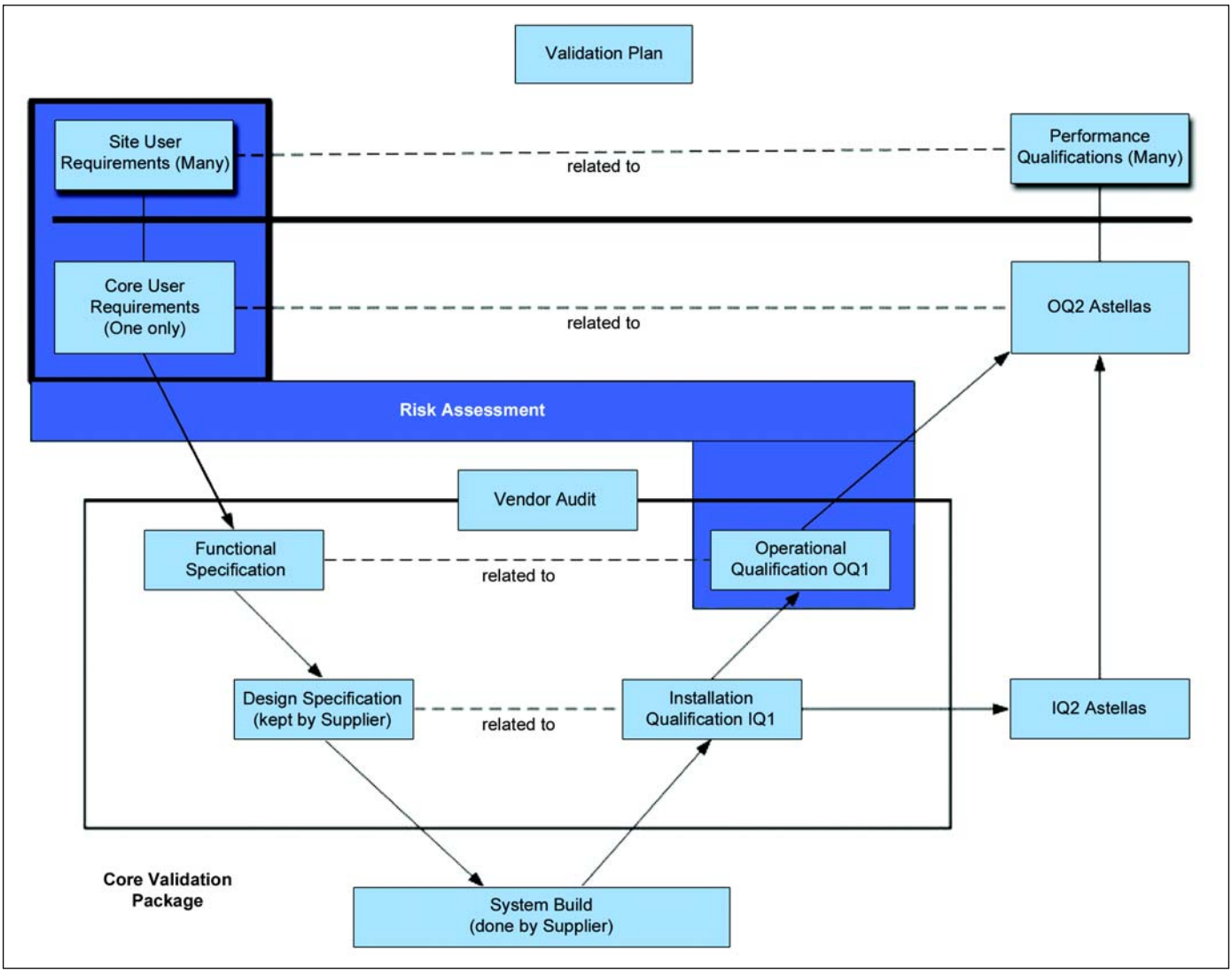

Figure 5. Overall V-Model.

was of great importance to the success of the project. A number of deficiencies were found that delayed initial acceptance of the supplier documentation and required immediate corrective actions.

The supplier, who subsequently worked very closely with the company in preparation of the detailed OQ2 technical protocols and other documentation, executed all requested actions during the project.

The audit also allowed the company to justify acceptance of existing supplier documentation (OQ1) for low impact business functions that were not repeated in OQ2.

Regulatory Background

The workflows implemented using the application are GMP critical and are used worldwide in business environments subject to applicable US Food and Drug Administration (FDA), European Union (EU), and Japanese regulations. Examination of the business and manufacturing processes regulated by GMP rules allowed identification of electronic records and electronic signatures and validation requirements for computerized systems. The assessment took account of all applicable regulations for the global system and matched them to the software system according to the intended use described in the User Requirements Specification (URS). In particular, the management of electronic records and signatures was examined and fully validated according to FDA expectations.

Risk Assessment

The purpose of the risk assessment was to focus validation on areas of the system that are most significant for product quality, safety, and records integrity with specific reference to applicable GMP regulations. The risk assessment was performed after completion of the core URS and was used as an input for customized development, OQ2 testing, and the design of workflows for PQ.

The effectiveness of risk mitigation was measured in both OQ2 and PQ by means of specific testing of the GMP functions that had been identified. All corrective actions were identified and implemented before release of the system.

Special consideration was given to the area of electronic signatures, which was fully tested in OQ2 according to the latest guidance from the FDA and the risk-based approach recommended by GAMP. No exceptions or areas of nonconformance were identified.

System	**CAPA and Tracking Systems – Department QA**									
Document Ref.	**GMP Risk Assessment**									**Corrective Actions for Risk Mitigation**
	GMP Risk	**Business Risk**	**Risk Scenario**	**Prof. Failure**	**Impact**	**Category**	**Prob. Detection**	**Priority**	**Acceptable**	
URS – CAPA and Tracking										
5.9 System Management	EU 4.9 EU 11.2 – 11.7 – 11.16 11.10 (e)	System management for the global organization may be difficult to manage, especially across time zones	- System management and privileged access might be performed by unauthorized persons without training - Changes made by the system administrator might not be authorized or recorded in a change log or other audit trail	M	H	1	L	H	No	(OQ) Verify training records of system managers (OQ) Verify that system management procedures exist and are followed, including records of all changes (PQ) Verify that system management services are acceptable for the time zone of that site
10.4 Incident	211.192	Incidents may not be examined according to GMP and corrective actions may not be implemented as required for the business process	- Incidents in production or other unexplained discrepancy may not be subject to proper review and investigation by QA, as necessary	L	H	2	H	L	No	(PQ) Ensure that incident management procedures exist and are followed, and agree with the signed and approved workflow (PQ) Verify that the agreed steps of the workflow have been effectively implemented
10.12 Request for Change	EU 4.3 EU 5.23 EU 11.11 211.68 (b)	Requests for change may not be examined according to GMP and may not be implemented as required for the business process	- Change control documents may not be approved, signed, and dated by appropriate persons - Significant changes to the manufacturing process or to computerized systems might not be validated	M	H	1	M	H	No	(PQ) Ensure that change management procedures exist and are followed, and agree with the signed and approved workflow (PQ) Verify that the agreed steps of the workflow have been effectively implemented

Table B. Extract from risk assessment.

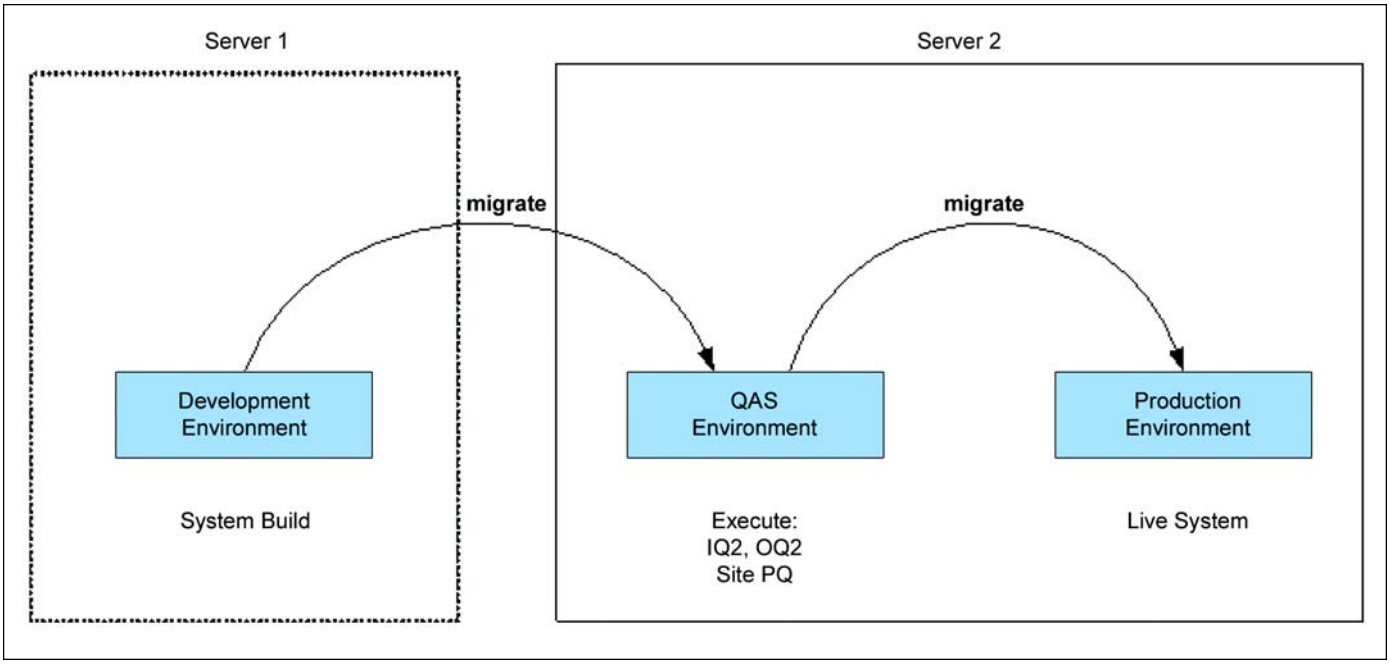

Figure 6. Server environments.

Risk Assessment Process

The assessment of risk is based on the identification of potential failure of a component or function, compared to the impact of such failure on the managed process. This assessment is based on the description of the system provided in the URS and the workflows as compared with the applicable GMP regulations for the process. In this way, the risk of noncompliance is greatly reduced and conformity with business requirements also is emphasized. The result is that the GMP critical areas of the URS and the workflows are clearly identified, showing applicable GMP paragraphs, business process, and analysis of GMP-business risk.

Effects of Risk Assessment

Reduced Test Volume

Analysis of the OQ1 tests from the supplier compared to the risk assessment allowed identification of the GMP critical OQ tests. The critical tests from OQ1 were repeated in OQ2 in the QAS environment and other tests were added to verify mitigation of GMP risks not addressed in OQ1. In this way, only 23% of the OQ1 testing needed to be repeated in OQ2.

Out of 217 tests in OQ1, 50 were repeated in OQ2 and a further 27 were added to verify specific GMP customizations.

Test Evidence for Business Process

The OQ1 tests from the supplier covered all aspects of the system, including both GMP and non-GMP areas. Since all GMP tests were repeated and given that the supplier assessment was found to be acceptable, the OQ1 test evidence was deemed acceptable for the remaining parts of the business process. In addition, the processes described in the workflows were individually tested in the PQ phase of the project for each site.

Extracts from Risk Assessment

Table B provides extracts from the risk assessment document, illustrating the effectiveness of the process.

Conclusion

The global pilot was successful from both a project and a business perspective with no deviations from corporate policies and standards. This led to rapid approval and acceptance of the new system as part of the new business management philosophy and an accelerated rollout across the corporation.

After implementation in March 2006, the following rollouts have taken place worldwide:

- Global Change Control – December 2006
- GCP Audit Management – August 2007

The following rollouts are planned:

- GMP Audit Management – December 2007
- Customer Complaints Management – Worldwide by April 2008

Acronym Glossary

CAPA	Corrective and Preventative Action
CFR	Code of Federal Regulations
ERP	Enterprise Resource Planning
GAMP	Good Automated Manufacturing Practice
GMP	Good Manufacturing Practice
OOS	Out of Specification
QAS	Quality Assurance System
QM	Quality Management
SOP	Standard Operating Procedure

References

The following were used as references during the project:

1. *GAMP® 4, Good Automated Manufacturing Practice (GAMP®) Guide for Validation of Automated Systems*, International Society for Pharmaceutical Engineering (ISPE), Fourth Edition, December 2001, www.ispe.org.
2. *GAMP® Good Practice Guide: IT Infrastructure Control and Compliance,* International Society for Pharmaceutical Engineering (ISPE), First Edition, August 2005, www.ispe.org.
3. *GAMP® Good Practice Guide: A Risk-Based Approach to Compliant Electronic Records and Signatures,* International Society for Pharmaceutical Engineering (ISPE), First Edition, April 2005, www.ispe.org.

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Use and Misuse of Capital Cost Estimate Contingency – Why Deleting it Makes Projects More Expensive, Not Less

by Gordon R. Lawrence

This article presents the general principles of what contingency and estimate accuracy are in order to remove common misconceptions about their composition and use.

Introduction

Investment of capital in new production or research facilities is a regular part of daily life for all major pharmaceutical firms. Before a decision to invest is made, an estimate of the costs to design, engineer, and construct the new facility must be made. Any estimate, by definition is imprecise and carries financial risks. The cost implications of that imprecision and those risks are reflected in the application of contingency to an estimate and in assigning an accuracy range to that estimate.

There is a great deal of confusion among business sponsors, end-users, and finance managers outside of the project/engineering group as to exactly what contingency is, what it is for, and how it differs from an estimate accuracy range. This lack of common understanding was exposed in an article by Baccarini,[1] in which he described the results of a brief *vox populi* on the subject of contingency, held at a project management conference. One possible reason for this confusion and lack of understanding is the fact that although there are many published articles discussing in great detail how to calculate contingency and estimate accuracy,[2] these articles (of necessity) contain a considerable amount of statistical terminology. This terminology can be off-putting to the layman. Another reason may be due to the fact that many people conflate design allowance and management reserve with project contingency.

There also is a tendency among finance and business groups to view contingency as evidence that the project team is inflating or "padding" the estimate to give itself an easy life. In an effort to remove this padding and ensure the project is built for a competitive cost, these groups very often decree that the contingency should be limited to a specific percentage of the estimate cost or even in extreme cases deleted from the estimate altogether.

This article presents the general principles of what contingency and estimate accuracy are in order to remove common misconceptions about their composition and use. It uses simple graphical descriptions in order to assist the reader in visualizing the concepts. It avoids as much statistical detail as possible, sticking to simple statistical terms that should be familiar to all (i.e., median and mode). The article also differentiates between design allowance, contingency, and management reserve.

The article then goes on to show that contingency is not the same as estimate accuracy, that it is an essential part of any estimate, that it

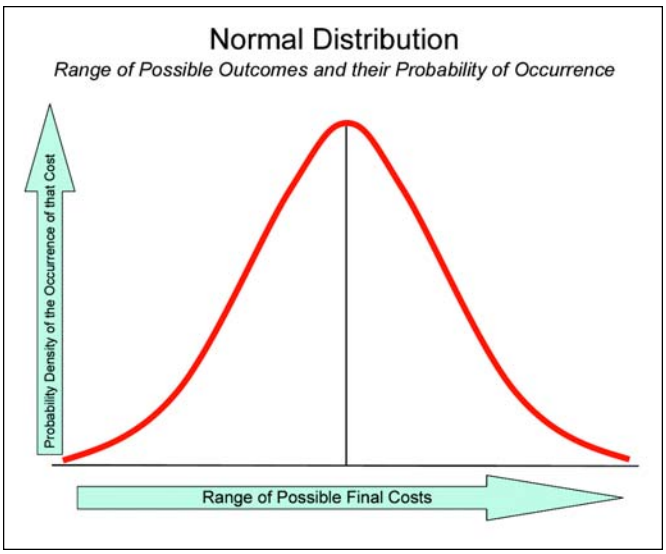

Figure 1. "Normal" distribution curve of possible cost outcomes.

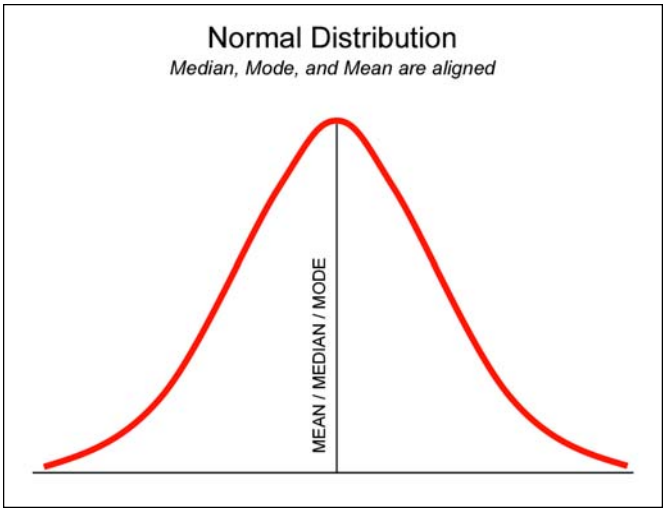

Figure 2. "Normal" distribution curve, showing mean, median, and mode.

should be expected that contingency will be totally consumed during the course of the project, that it does not include design allowances, and that contingency is not to be used for scope changes.

In addition, the article will address the issue of imposing artificial constraints on how much contingency a project team is allowed to retain in an estimate, in the belief that this will ensure that the final project cost will be competitive. The article will explain why taking such action can be counterproductive and result in projects becoming less cost competitive instead of more competitive.

Readers of this article should come away with a greater appreciation of the need for contingency and its difference from estimate accuracy. Those readers who then wish to take the next step and consider the practicalities behind calculating contingency and estimate accuracy for a specific project can use the list of references at the end of this article as a starting point.

Estimate Range

Why is an Estimate Range Necessary?

A cost estimate is a prediction of what the final cost will be at some time in the future. Since it is impossible to accurately predict the future, any estimate has some risk and surrounding uncertainty. The range around an estimate reflects that uncertainty.

What is an Estimate Range?

The Estimator and the "Most Likely" Outcome

In single-point estimating, the estimator assigns a single cost value to the estimate. But picking a single point or in effect stating "the project will cost this much; no more; no less," clearly does not take into account that this is an estimate with surrounding uncertainty. So what is this single point value? As Querns[3] and Yeo[4] both confirm, it is generally recognized that estimators tend to pick the "most likely" value when asked to choose a single point.

Three-point estimating takes more account than single point estimating does of the fact that there is some uncertainty around the estimated cost. It asks the estimator to specify a minimum and a maximum cost based on his/her experience, as well as the "most likely" cost.

Armed with this information and by taking a view (a) on the potential monetary effect of a risk on the cost, coupled with (b) the likelihood of the occurrence of that risk, a probability distribution curve of the range of cost outcomes can be developed. If the range of possible outcomes is normally distributed, it will look like the example in Figure 1.

At this point, we introduce our first statistical term, the "most likely" (or the most popular) outcome is the mode of the set.

Choosing the 50/50 Outcome

As noted by Hackney,[5] Healy,[6] and others, it is generally agreed that the best all-purpose estimate for project management and control purposes is the even-chance or 50/50 outcome value. (i.e., the value at which there is a 50% chance of overrunning or underrunning the estimate figure).

The reason why management should choose to ask project teams to control to the 50/50 outcome becomes clear if one considers that management is concerned with not just one, but a portfolio of projects. If a corporation has multiple projects ongoing, controlling each project to greater than the 50/50 point means that management will have more funds committed to projects than (on average) the projects will ultimately need. Hence, funds are tied up unnecessarily and the overall number of projects that could be tackled is reduced. Conversely, controlling to less than the 50/50 point means that, on average, most projects will overrun their budgets, making portfolio budget management difficult as demand for funds fluctuates. In addition, more projects may be authorized than there are ultimately funds for because an optimistic view has been taken of the amount of funds each project requires.

The "Most Likely" and the 50/50 Outcome

To put the 50/50 outcome another way, it is the point where there are an equal number of possible outcomes on either side of the estimate value. Hence, in basic statistical terms, the 50/50 outcome is the median.

If the data set of possible cost outcomes for the overall cost estimate of the project is normally distributed, then as seen in Figure 2, the mode or the "most likely" value, as developed by the estimator, and the median or the 50/50 outcome, as desired by management, are both at the same point on the curve (along with the mean, or the average cost).

Estimate Accuracy Ranges

If someone says an estimate has a ±10% accuracy, what does this mean?

Any discussion of the percentage accuracy must be related to a specified confidence interval. To use Figure 3 as an example, the median/mean/mode cost is $100 million. The 80% confidence interval in this example (i.e., the confidence that the actual cost will fall within this range 80 times out of 100) corresponds to costs between $90 and $110 million (i.e.,

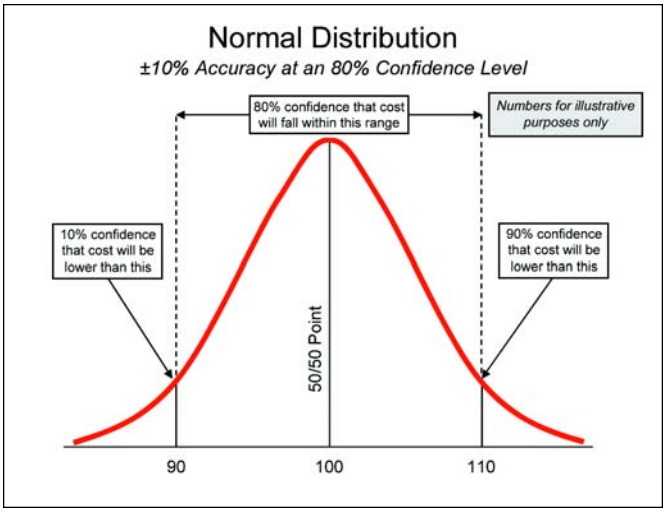

Figure 3. "Normal" distribution curve with example numbers (for illustration purposes only).

the actual cost will turn out to be below $90 million only 10 times out of 100 and above $110 million only 10 times out of 100).

The difference between $100 million and $90 million or between $100 million and $110 million is in each case 10% Hence, this (illustrative) example estimate has a +10% and –10% accuracy with 80% confidence.

An 80% confidence interval is used purely for illustrative purposes. Project teams may choose the 90% confidence interval, or some other interval that suits the corporation's attitude to risk. (Engineering and cost estimating personnel tend to use confidence intervals, such as the 80% confidence interval. However, statisticians and economists sometimes prefer to refer to a standard deviation range. In which case, the 80% confidence range is equal to ±1.28 standard deviations).

Cost Contingency

Having described cost estimate accuracy ranges, the following discussion will focus on cost contingency to see how this differs from an estimate range.

What is Contingency?

Written Definitions of Contingency

Baccarini noted a lack of understanding of contingency; however, although there is a lack of common understanding on the *detail* of what contingency means, Baccarini also noted that there is general agreement that contingency is a sum of money added to a capital cost estimate to cover certain uncertainties and risks in a capital cost estimate. Taking this point further, consider the de-facto industry standard for project management in the USA (and to some extent globally); the *Project Management Body of Knowledge*.[7] This reference book describes contingency as: *"A provision in the project management plan to mitigate cost risk."* The Association for the Advancement of Cost Engineering International (AACE-I) performs a similar role for cost engineering in that its recommended practices also are de-facto USA (and global) industry standards. The AACE-I recommended practice covering cost engineering terminology[8] defines contingency as: *"An amount added to an estimate to allow for items, conditions, or events for which the state, occurrence and / or effect is uncertain and that experience shows will likely result, in aggregate, in additional costs."* In this article, we are following the consensus then if we describe contingency as: *"An amount of money for goods and services which at the current state of project definition cannot be accurately quantified, but which history and experience show will be necessary to achieve the given project scope."*[9]

Several authors, including Karlsen and Lereim[10] note that many sources use terminology that does not make sufficient distinction between design allowances (for items that experience has found to be systematically required[11]), contingency, and management reserve. In this discussion, a clear distinction will be made between the three elements.

In order to provide some detail around that general definition, the following discussion will focus on a graphical description of contingency.

Project Contingency – Why the Most Likely Cost is not the 50/50 outcome

In the previous discussion of estimate accuracy ranges, a normal distribution of possible outcomes was assumed; therefore, the most likely cost (the mode) was the same as the 50/50 outcome (the median). However, as with many things where the cost cannot be less than zero, but the upper limit is less well-defined, the range of possible outcomes for an estimated cost is right skewed - *Figure 4*.

This being the case, the mode, median, and mean are no longer in alignment. In fact, the median is now a larger cost outcome than the mode. (In addition, it is now clear that when describing an estimate range, it is rare that the plus and minus percentages will be the same.)

Since the estimator has produced a base estimate that corresponds to the mode and it is assumed that the estimate is required to have a 50/50 outcome (the median), there is a gap (the median value minus the mode value) that needs to

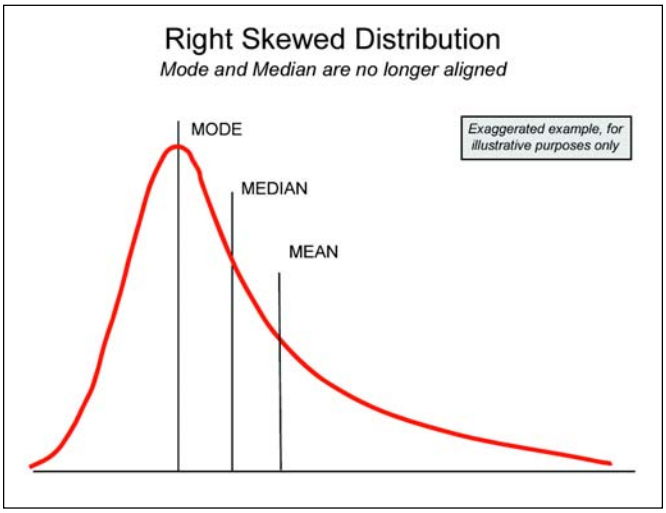

Figure 4. "Right Skewed" distribution, showing how mean, median, and mode no longer align.

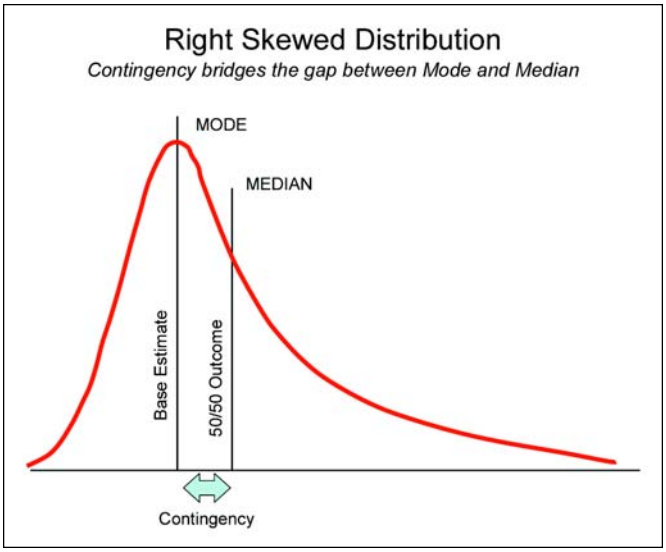

Figure 5. "Right Skewed" distribution, showing how contingency bridges the gap between mode and median.

be filled. As shown in Figure 5, it is to fill this gap that ***project contingency*** money is applied to the estimate.

The question may arise, why doesn't the estimator pick the median value instead of the "most likely," or mode value for each item; or in other words, isn't the need for contingency simply the result of poor estimating on the part of the estimator. The answer to this is an emphatic "no." The estimator can add a design allowance to an individual estimate line item if history shows that an allowance is systematically required for that item. However, contingency is to cover additions that cannot be systematically assigned to any one line item in an estimate, but which, based on historical evidence, can, as noted in the AACE-I definition quoted earlier, be seen to be required "*in aggregate,*" over the entire estimate. Consequently, the act of including the correct amount of contingency is a sign of good, not poor estimating.

It now becomes clear that:

- When calculating the "most likely" outcome, the estimator will already include design allowances for items that have been found to be systematically required. Hence, *design allowances are a part of the estimator's base estimate* (his "most likely" estimate) and are not part of contingency.
- Since the distribution curve reflects only the project scope, contingency is only for the scope as defined in the estimate. *It is not intended to cover scope changes*.
- Contingency is not the same as estimate accuracy
- Contingency is required if the estimate is to reflect a 50/50 likelihood of over or underrun.
- Since contingency is required in order to reach the 50/50 point, *contingency should be expected to be consumed as a normal part of a project* (since 50% of the time all contingency will be consumed).

Management Reserve – Achieving Predictability

The question then arises, what if the organization values cost predictability and wishes to know not just the 50/50 probable outcome, but an outcome with a greater than 50% probability of being underrun; for example, the 90/10 outcome (i.e., a 90% chance of being less than the specified cost). In this case, the estimate value should be the one that lies at the maximum of the 80% confidence interval. A management reserve would then be needed on top of the project contingency to cover the difference between the 50/50 outcome and the 90/10 outcome, ensuring a 90% probability of underrunning - *Figure 6*.

It is important to note here that this management reserve, just like the project contingency, is based on the specific project scope. Hence, just like contingency, it is a reserve to ensure predictability. *Management reserve is not a fund for scope changes.* A further question then arises; why isn't management reserve just included with contingency? The answer to this lies in two parts.

First, as mentioned earlier, it makes cost efficient sense to control estimates to the 50/50 point. Sometimes an individual project will have a higher cost, sometimes lower. But nevertheless, on average, the projects within the portfolio will come in on budget; therefore, no more or less money is assigned than is necessary. Consequently, for the sake of the overall portfolio of projects, there is value in asking the project manager to control to that point (with the proviso that he is not automatically censured for overrunning since 50% of the time he will overrun.)

Second, whereas there is a 50% chance of contingency being completely consumed, there is a less than 50% chance of the management reserve being consumed. Since this is the case, it makes sense to keep those funds out of the control of the project team and only release them to the team on an as required basis.

How Much Contingency is Needed?

Methods of Calculating Contingency Requirements

Although contingency and estimate accuracy can be graphically illustrated by the use of a distribution curve and the

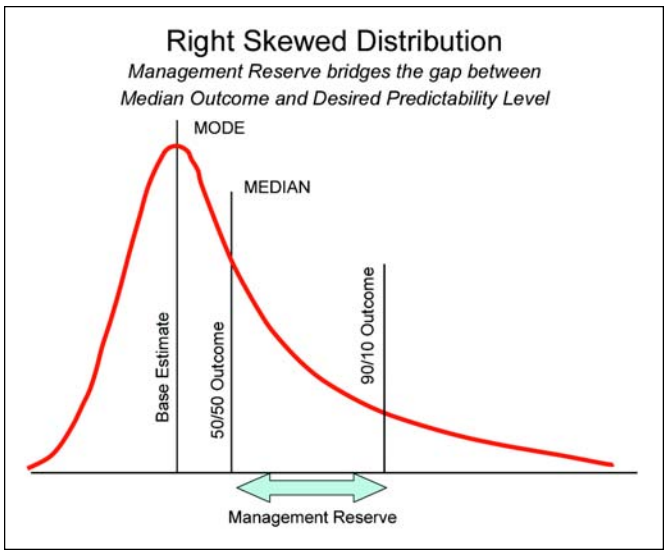

Figure 6. "Right Skewed" distribution, showing how management reserve bridges the gap between the 50/50 outcome and the desired level of predictability.

mode and median, it should be obvious by now that the calculation of the shape of that distribution curve takes considerable estimating experience (in order to form an opinion on possible risk drivers, outcomes, and probabilities) and statistical knowledge (to calculate the curve from that information). It is in calculating this curve and the probability ranges around the estimate that techniques such as risk analysis and Monte-Carlo simulation are brought into play.

However, such analysis and simulation requires specialist knowledge and effort, as well as time to perform the calculations. This may not always be available. Consequently, although a full statistical analysis of risk probability might be the obvious route to take, in practice, there are at least two other common methods. These are:

- Setting a predetermined percentage – Some companies mandate that all estimates will include a pre-determined percentage of the base estimate (such as 5 or 10%) as contingency.
- Expert Judgment – Where skilled and experienced estimators and project team members assign a level of contingency that they believe to be appropriate, based on their experience.

An interesting article by Burroughs and Juntima[12] examines all three methods and compares them to a fourth method; calculation of contingency using a statistical model based on regression analysis of past project results. They found that predetermined percentages and expert judgment methods worked with approximately the same level of efficiency as each other and were impervious to the level of project definition. Risk analysis methods provided a slightly better median performance than predetermined percentages or expert judgment, when project definition was good, but markedly worse performance when project definition was poor. The obvious lesson being that risk analysis is only as good as the base data fed to it.

The fourth method that Burroughs and Juntima propose, that of a regression model, appears to offer as good if not better results than the other methods, but it does require collection and collation of project data over a considerable period of time. (Although one could argue that this is merely putting into systematic form the "experience gathering" of the expert judgment method.)

A recent article by Hollman[13] examines these issues further. He discusses the drawbacks of Monte-Carlo simulations, as currently practiced, and ways in which regression models can be incorporated into the risk analysis and contingency calculation process.

Methods of Reducing Contingency Requirements

Knowing that project contingency is the difference between the mode and the median, it now becomes clear that different levels of project contingency (and management reserve) will be required for different shapes of risk distribution curves. The less risk and uncertainty there is around a project, the more the range of probabilities can be reduced, the "sharpness" of the distribution curve increased, and the gap between the median and the mode reduced - *Figure 7*.

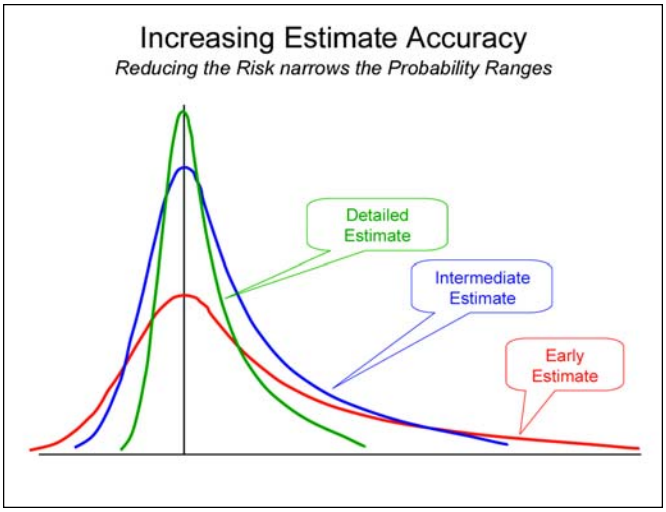

Figure 7. Reducing risk reduces the range and the contingency requirement.

The question then arises, how can risk and uncertainty be reduced? As discussed by Hollmann, project risk and uncertainty arises from several distinct elements, including systemic risks and project-specific risks.

Project Systemic Risks

Systemic risks are those that result from characteristics of the project or process "system." Two of the systemic risks are of paramount importance because they are often the predominate drivers of cost growth. These two elements are:

1. the level of completeness of the project front end definition
2. the project type

(This two element aspect of cost uncertainty has been discussed in numerous studies, including Merrow and Yarossi[14] and Burroughs and Juntima). Of these two elements, project front end definition is clearly within the control of the project team, while project type is largely outside the control of the team.

1. Project Front End Definition

A cost estimator prepares an estimate based on the scope of work documents supplied to him/her. Therefore, any items omitted from that scope of work will not be picked up by the estimator and will remain as potential risks to the project cost outcome. Similarly, any ill-defined items will carry greater risk than clearly defined items.

This point is most obvious in the fact that estimate accuracy ranges are universally understood to narrow as the project design, engineering, and construction proceeds. The more that the design, engineering and construction is complete, the more is definitively known and the less risk and uncertainty there is in the estimate. Ultimately, once the project is complete, the final costs are known and there is no

risk and uncertainty left. Several organizations, including the AACE-I have produced documents classifying estimate types, and describing the approximate estimate accuracy range to expect, based on the level of front end development of the design package[15].

The point also is made indirectly in the two industry standards for assessing project front end definition, the Construction Industry Institute (CII) Project Definition Rating Index (PDRI)[16] and the Independent Project Analysis (IPA) Front End Loading (FEL) Index.[17] Both of these indices look at how well developed a project front end design package is at the time of developing the estimate. The point being that if the package development can be improved, this will reduce risk on the project; therefore, reducing the estimate accuracy range, reducing the amount of contingency needed, and increasing the probability of having a competitive, predictable project.

2. Project Type

A project that is using new technology carries greater design and execution risks than a project to build a facility that contains no new process technology and that uses processes and equipment that are tried and tested. Similarly, a project with greater complexity (for example, more unit operations) will carry greater design and execution risks than a simple project. These types of projects will require greater levels of contingency, as has been shown in the statistical models described by Merrow and Yarossi and Burroughs and Juntima.

Project-Specific Risks

Project-specific risks are those drivers that are unique to a given project's scope or strategy (e.g., the weather, labor markets, etc.). In some cases, these risk drivers may be predominant, and they can only be identified through risk analysis. By the time an authorization estimate is prepared, it is hoped that the impact of project-specific risks will have been largely mitigated through effective front-end planning (which also reduces the systemic risks).

The Effect of Limiting or Deleting Contingency

Project contingency is a necessary requirement for an estimate with a 50/50 probability of over or underrun. Consequently, it is clearly not "padding" and in addition, it should be clear that 50% of the time it will be completely consumed during the course of the project. Also, the amount of contingency required is a function of the risk associated with both the project characteristics and the level of scope definition.

Therefore, what happens if the contingency is artificially fixed at a value lower than that which is required? (e.g., if the company has a blanket rule that contingency will only be 5% on all project estimates, but the project team has calculated that a contingency of 15% is required on their project). Or what if the contingency listed by the project team in their estimate is subsequently reduced or removed by financial management staff in the belief that contingency is unnecessary "padding" and that removing it will ensure that the project cost remains competitive?

The first point to note is that by reducing/removing contingency, the financial management team is sending a very clear message to the project team that it is not trusted to estimate costs accurately. The second point to note is that if the estimate has been prepared correctly then by deleting contingency, the project is immediately condemned to having a greater than 50% probability of overrunning.

The next situation to consider is what if this organization also is the type of organization that values cost predictability and punishes overruns? This means that in order to provide greater certainty of avoiding an overrun, both contingency and reserve are required. But the project team knows that any contingency or reserve clearly labeled as such will be removed. Consequently, the team has *only one rational course of action*. That is to include contingency and reserve in the estimate, but hide it among the estimate line items.

Hiding contingency and reserve in the estimate has three effects. First, it sets the stage for a culture of weakened and less accurate estimating. Second, it weakens project control because control budgets will no longer reflect the expected requirements for hours or cost. Consequently, change management is likely to be performed in a less disciplined way. Third, human nature being what it is, the reserve money is no longer at a less than 50% likelihood of being spent. Since it is hidden in the budget it is more likely to be spent, leading to a trend of less cost competitive projects within the portfolio.

In addition, such a situation is typically accompanied by a lack of independent checks on the estimate (otherwise, the hidden contingency would be discovered and questioned). Consequently, the natural temptation within the project team is to hide not just sufficient contingency and reserve money to ensure a 90/10 probability of underrun, but a 95/5 probability or even higher. As already mentioned, once funds are hidden in an estimate in this way, they almost inevitably get spent.

Thus, by removing contingency in order to try and ensure that "padding" is removed from the budget, financial teams actually encourage "padding" to be put in; which was exactly the opposite of their intention. This "padding" is hidden, which will contribute to degraded control of the project overall (which adds greater risk) and since it is hidden, it is more likely to be spent. All of this tends to lead to less cost competitive project outcomes.

Conclusion

Cost estimates are by their nature predictions of a future outcome. As with any prediction, they carry risks and uncertainties. Using experience as to the cost effect of a project risk and its likelihood of occurrence, coupled with risk probability mechanisms such as Monte-Carlo simulations to combine risk effects, a range of possible cost outcomes can be developed.

Estimate accuracy is a function of that range of possible outcomes and should always be expressed with reference to a level of desired probability (e.g., this is a ±10% estimate, within an 80% probability range).

When managing a portfolio of projects, the logical estimate control point for individual projects is the 50/50 outcome since although 50% of projects will overrun, 50% will underrun and the overall average is neutral and neither too many or too few funds are committed overall.

The need for project cost contingency arises because the set of possible cost outcomes is not normally distributed. Contingency bridges the gap between the base estimate calculation (the "most likely" point, or the mode) and the outcome probability point that the project team is expected to control to (usually the 50/50 outcome point, or the median).

Thus, it becomes clear that:

- Design allowances are not part of contingency.
- Contingency is required in order to ensure a 50/50 likelihood of over or underrun.
- Contingency is not the same as estimate accuracy.
- Contingency should be expected to be consumed since 50% of the time it will be totally consumed.
- Contingency is not a fund for scope changes since it is related purely to the project scope as estimated.

If management requires greater cost predictability than a 50% chance of underunning, it needs to retain a management reserve representing the difference between the 50/50 probability point that the project team is controlling to and the outcome probability point that management desires. Management reserve also is not a fund for scope changes since it too is related purely to the project scope as estimated.

Improving the project definition level can reduce the amount of contingency monies required, but projects that by their very nature are risky (e.g., new technology projects) will inevitably require more contingency than more straightforward projects.

A rational human desire to meet targets and avoid censure due to overruns means that artificially reducing or deleting contingency in cost estimates in the hope that this will reduce cost "padding" and encourage competitive final costs tends to have exactly the opposite effect.

A better way to ensure competitive cost outcomes is to encourage open and honest cost estimating with full declaration of contingency monies (calculated on the basis of risk analysis) and to encourage very good front end definition before development of the authorization estimate.

In summary, the advice for finance managers is:

- Trust your project teams to produce transparent estimates.
- Allow them to clearly show contingency (which is based on analysis of the risks).
- To reduce and control costs, focus on ensuring good design definition during the front end and on effective change and contingency management during execution. Do not focus on cutting contingency.

The advice for business sponsors and end users is:

- Don't use contingency to fund scope changes.
- If the need for scope changes occurs, accept that these are outside the project budget and must be estimated separately.
- Spend your effort on the front end design definition, making sure that the scope definition is agreed and as complete as possible before the estimate is completed.

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Dynamic Simulation in Pharmaceutical Operations

by Joseph S. Fox and Dustin Teschke

This article highlights dynamic simulation as a tool for improving capital utilization and Overall Equipment Efficiency (OEE).

Introduction

Much has been said about the current challenges facing pharmaceutical manufacturing. The escalating cost of new drugs has put a premium on time to market, and manufacturing ramp-up time. Current industry manufacturing practice is characterized by inefficient batch processes, high inventory costs, and long process dwell times due to release testing. Scrap rates are much higher – up to 50% for some products – than those experienced in more mature manufacturing environments. Compared to other industrial sectors, capital utilization rates are low and the cost of quality is high.[1,2,3]

Data from the Department of Labor Statistics shows that pharmaceutical manufacturing productivity lags other industries and the manufacturing sector average, and has done so for years. Output per unit of capital and multifactor productivity measures reinforce the notion that pharmaceutical manufacturing efficiency has historically taken a back seat to other industry concerns - *Figure 1*.

Much remains to be learned from other industries. This article highlights dynamic simulation as a tool for improving capital utilization and Overall Equipment Efficiency (OEE). OEE is a measure of the time that a manufacturing system is actually processing good product, and is the product of actual system availability, system performance, and product yield. Simulation will be an indispensable part of the pharmaceutical manufacturing "tool kit" as it develops a 21st century manufacturing model based on higher OEEs.

Dynamic Simulation

A simulation is a computer-generated model that represents in mathematical terms, the operation of a real or proposed manufacturing system. Computer-generated dynamic simulations describe over a defined period of time and usually in a graphic format the functional relationships between resources in the system.

As shown in Figure 2, dynamic simulations most commonly used in manufacturing are:

- Discrete-event simulation – those driven by a sequence of events occurring in discrete moments in time.
- Continuous simulation – simulation that is driven by a clock incrementing at a common rate, i.e., at fixed time intervals.

Moreover, discrete and continuous simulations can be driven by either stochastic or deterministic models:

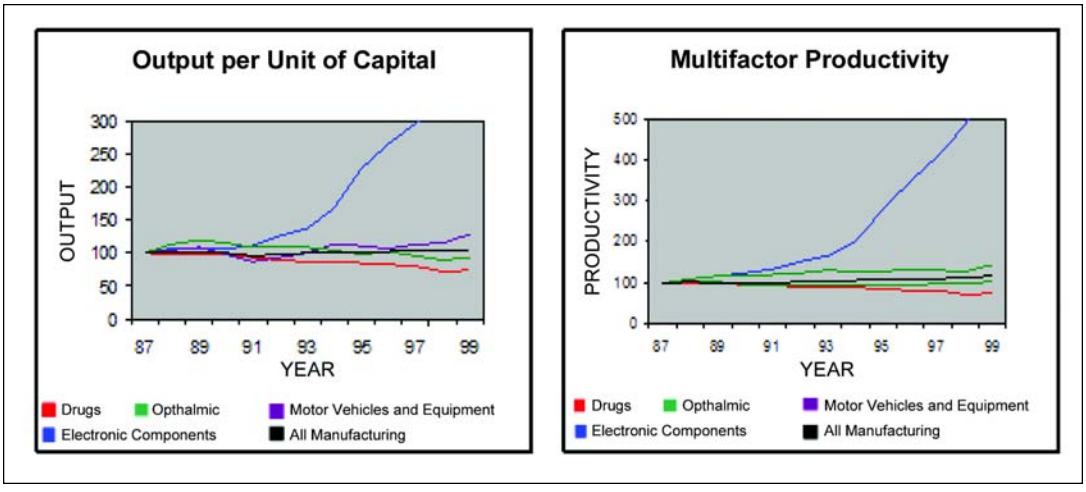

Figure 1. Output per unit of capital and multifactor productivity measures. (Source: compiled from the US Dept. Labor Statistics 2005)

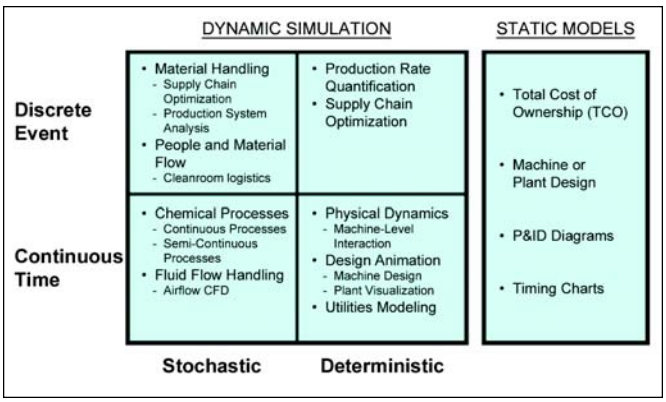

Figure 2. Dynamic simulations most commonly used in manufacturing.[13]

- Stochastic model – one that has at least one random input variable and one that requires statistical analysis of results.
- Deterministic model – a model whose input variables take particular rather than random values and whose output is identical for a given set of input.

Discrete event stochastic dynamic simulation – the subject of this article – predicts how process variables can change with time when moving from one steady-state to another or during a transient upset. In this, it differs from animation. Such dynamic simulation is commonly used to provide a window into the future in a way that permits better knowledge of the discrete event process. The technology allows "what if" scenarios to be developed, and is most often used to evaluate and then optimize system performance and functionality.

Dynamic simulations of this type are surrogates for physical experimentation with prototypes or full production systems. In comparison with prototyping or production trials, they have the advantage of time compression, physical scaling, and experimental control.

The technology provides a means to avoid or at least better manage risk. It can: clarify and decompose feasible paths from system design to implementation; test resource assumptions; determine the effect of the design on standard operating procedures and vice versa; identify implementation risks, and plan continuous improvement opportunities.

Manufacturing inputs that are required to create a dynamic simulation include: system operating parameters (e.g., machine throughput, conveyor lengths); control logic parameters (e.g., sensor locations, fault handling logic); system reliability parameters (e.g., mean time between failure, mean time to recover); and system procedural parameters (e.g., input material scheduling, operator scheduling). The system's operating and control logic parameters are modeled as discrete values and taken from the system's design. Conversely, the system's reliability and procedural parameters must be calculated or observed – and should define probability distributions rather than discrete values. Reliability and procedural data can be collected either from a system's Programmable Logic Controller (PLC) or Supervisory Control and Data Acquisition (SCADA) systems, or from time and motion studies. A variety of scenarios are normally simulated and compared to the current scenario – the "baseline" – in order to arrive at an optimum.

The simulation case histories described below were run with Arena Factory Analyzer.™ This package uses a flow chart approach to the modeling of dynamic processes, and is capable of importing many forms of pre-existing engineering data. Models produced represent detailed documentation of the process being investigated, while model output can be viewed either in detailed quantitative reports or in the form of graphics to verify and benchmark the process. It can communicate with external devices, making it a useful real-time process emulation tool. Other packages with good discrete event dynamic simulation capability include ProModel,™ Simul8,™ and WITNESS.™

Dynamic Simulation in Pharmaceutical Planning and Operations

Discrete event stochastic dynamic simulation is widely used in the optimization of manufacturing lines in the automotive industry. In semiconductors, such dynamic simulation is used to predict time-dependent interactions of equipment, processes, sensors, and controls systems as well as to optimize equipment systems and process recipes. It also is used to model interactions between semiconductor batch size, cycle rate, and Work-In-Progress (WIP) levels, as well as a means of performing sensitivity analyses of differing operating policies.[4,5,6,7]

Although simulation in pharmaceuticals is not new, it has been applied mostly to continuous event bulk processes and to visualize facility design.[8,9,10] Little has been written on the dynamic simulation of discrete material flows in either upstream or downstream operations, or on the value of simulation to cGMP and quality by design.

GMPs require, among other things, that manufacturing plants must be in a "state of control." It also requires quality systems to be in place not only to detect and prevent problems, but also to analyze root causes of failure. GMPs require systems that lead to continuous improvement. Further, the FDA has recently re-assessed its approach to GMPs, emphasizing processes knowledge and process risk.

Current quality by design initiatives are intended to augment cGMPs. In particular, ICH Q8 is directed toward a proactive, science-based approach to process development and to real-time quality assurance. It calls for continuous improvement in the understanding of manufacturing processes in relation to a pre-defined process "design space."[11,12]

It can be argued that well conceived dynamic simulation is a powerful tool whereby the "desired state" or "design space" of a process – and the probability of deviation from a desired state – can be proactively identified, assessed, and measured for risk. Simulations also can contribute to process emulation – comparing real and idealized operation in real time, thereby assisting in the assurance of consistent quality. Indeed, it is suggested that dynamic simulation is potentially one of the most powerful tools for simultaneously achieving and assuring quality, improving efficiency, and implementing cGMPs[13] and ICH Q8.

The more knowledgeable we are about areas of process risk, the more we can focus on the most critical aspects of a process, and apply more rigorous technical change and monitoring. Hence, an important objective in cGMPs should be the development of structured, quantitative models that capture the cause and effect relationship between high risk process variables and outcomes – i.e., models that are capable of managerial "what if" analysis. Because operational risk varies from plant to plant and process to process, simulation models and the concomitant need for data collection must necessarily be customized.

Assuming robust and realistic models, situations where dynamic simulation can directly address GMP issues include:

- Reject analysis – rejects or product non-conformances suggest loss of process control. Simulation can rapidly uncover root causes.
- Change control – evaluating the impact of change on process and its control.
- Manufacturing fault recovery – cGMP dictates that faults, when they occur, must be investigated qualitatively and quantitatively described and that preventative methods developed to prevent re-occurrence.
- Modeling of validated batch time limits – optimizing the balance between process time, capital investment, and drug stability, before capital investment.
- Assessing product traceability – modeling accumulation to ensure conformance with FIFO principles.
- People and material flow modeling – balancing flow with the ability of a sterile facility (as well as the environments around equipment) to recover.
- training and qualification

Dynamic Simulation and Solid Dose Packaging Optimization

Within existing pharmaceutical operations, production line simulation is valuable when operations are unable to supply the required production volumes from existing capital equipment. When faced with product shortages, it is essential to identify the rate limiting factors. "Know-how" is not good enough – production operations need to "know why" and "need to know now."

Dynamic simulation allows an objective review of the situation. This is especially true in the pharmaceutical industry, where standard product vendors deliver stand-alone, single-purpose machines, often without supervisory control systems or in-line accumulation. As a result, one upset can lead to chain reactions and significant downtime.

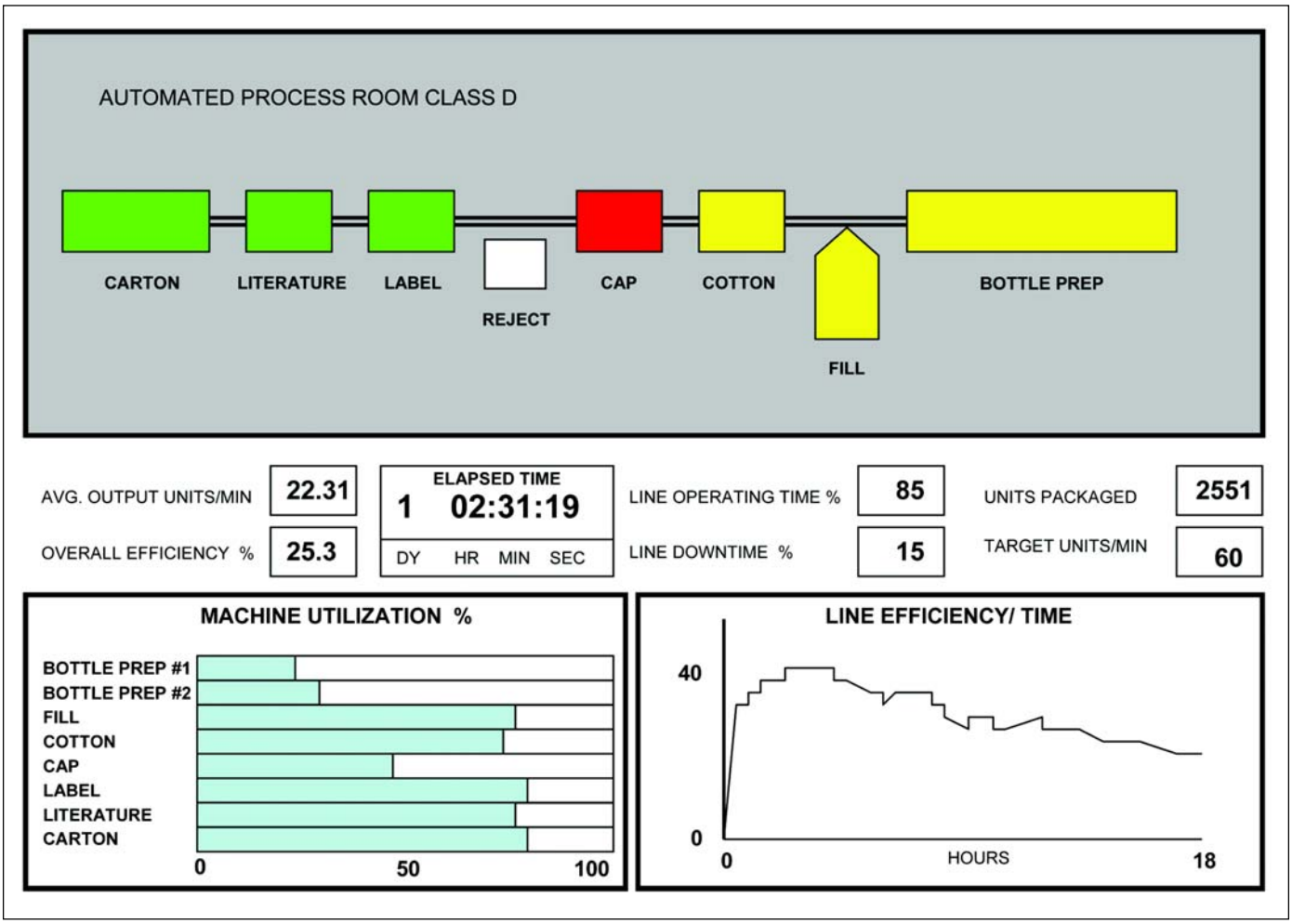

Figure 3a. Baseline simulation model.

This situation is illustrated here in a hypothetical case of a solid dose filling and packaging line, based loosely on a number of lines that we've seen. In its base state, the line was characterized by an unacceptably low OEE.

After performing time and motion studies on the line, a technician was able to quickly create a baseline simulation model - *Figure 3a*. Simulated baseline performance was observed using an accelerated clock, quantifying a known low OEE (declining from a steady state 37% to 21% as line errors accumulate over time). It also confirmed a material flow bottleneck before the existing tablet feeder, as well as other areas of line imbalance further downstream.

This baseline model allowed the construction of a variety of alternatives. Production staff close to the process had hypotheses that need to be tested, and several "what-if" analyses were programmed and run before arriving at the optimum.

A number of simulation iterations were run with this input. Not all of the proposed changes were found to be favorable. For example, it was originally thought that greater throughput might be achieved by adding a higher capacity filler, whereas through simulation this action was found to push the pre-filler bottleneck downstream to labeling without any significant increase in OEE. The "what-if" simulation provided the "know why" and prevented costly and time consuming "on-line" experiments.

A simulation optimum ensued, as did a plan of action for process improvement. The plan included the provision of the higher capacity filler, a second labeler, as well as 30 seconds of pre-label accumulation - *Figure 3b*. Altogether, the simulated optimum resulted in a significant OEE increase for the line – beginning at 65%, falling over time to 41% – as well as considerably better line balance and product throughput. Lifecycle cost calculations (not shown here) showed a 50% decrease in unit lifecycle cost and a half year payback on the cost of the improvements.

Simulation and Biopharmaceutical Scheduling

Roller bottle systems are applied to certain bioprocessing operations involving animal cell and viral cell culture applications. They may be the conscious choice for anchorage dependent, fastidious, or fragile micro-organisms cells such as primary cells. Roller bottle processing may be chosen where bio-molecular product cannot be supported in the stirred submerged culture of a bioreactor. They may be used for historical product development reasons or where there are regulatory arguments in favor of scale-up from roller bottle

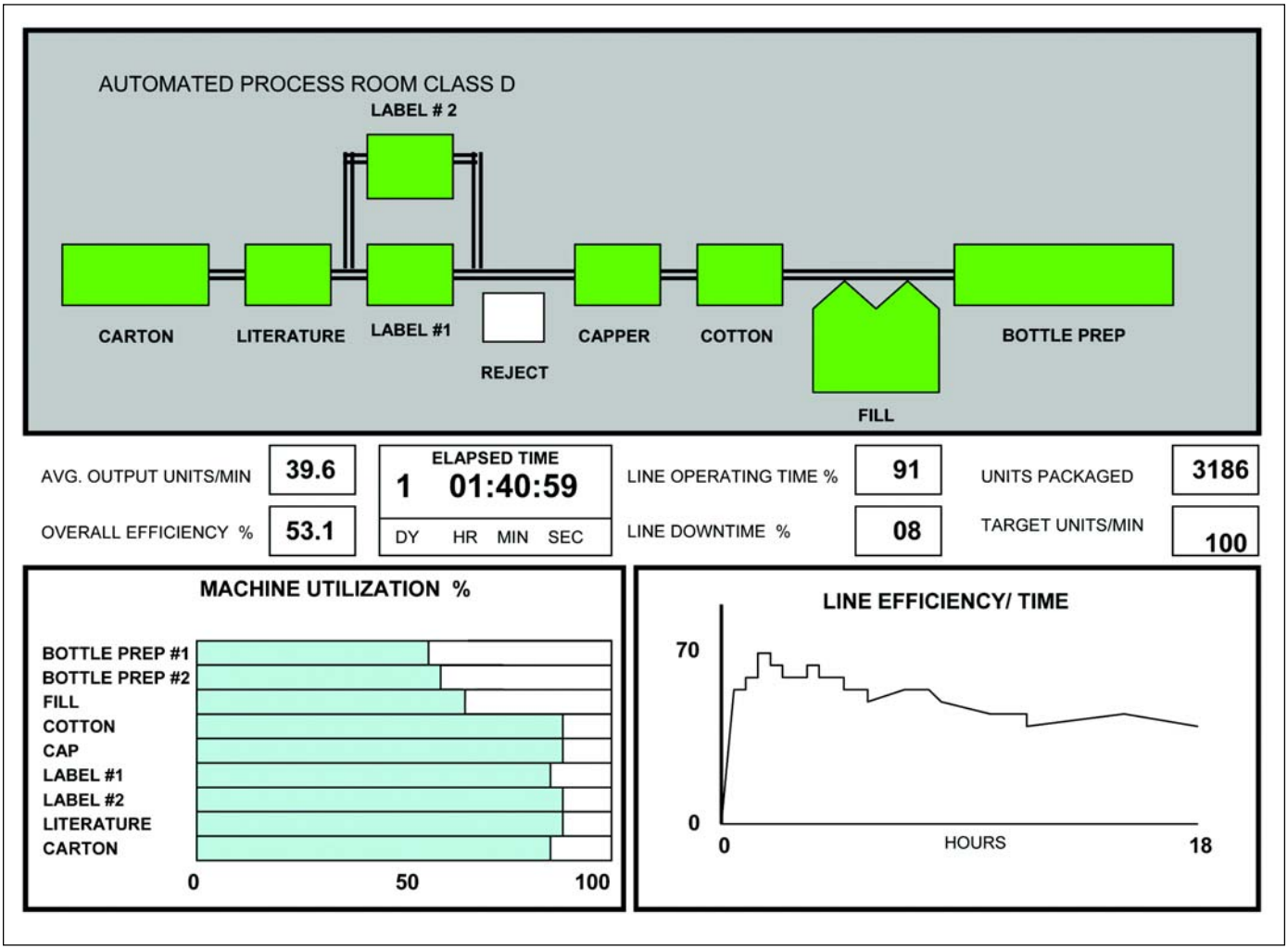

Figure 3b. Solid dose bottling line – optimized state.

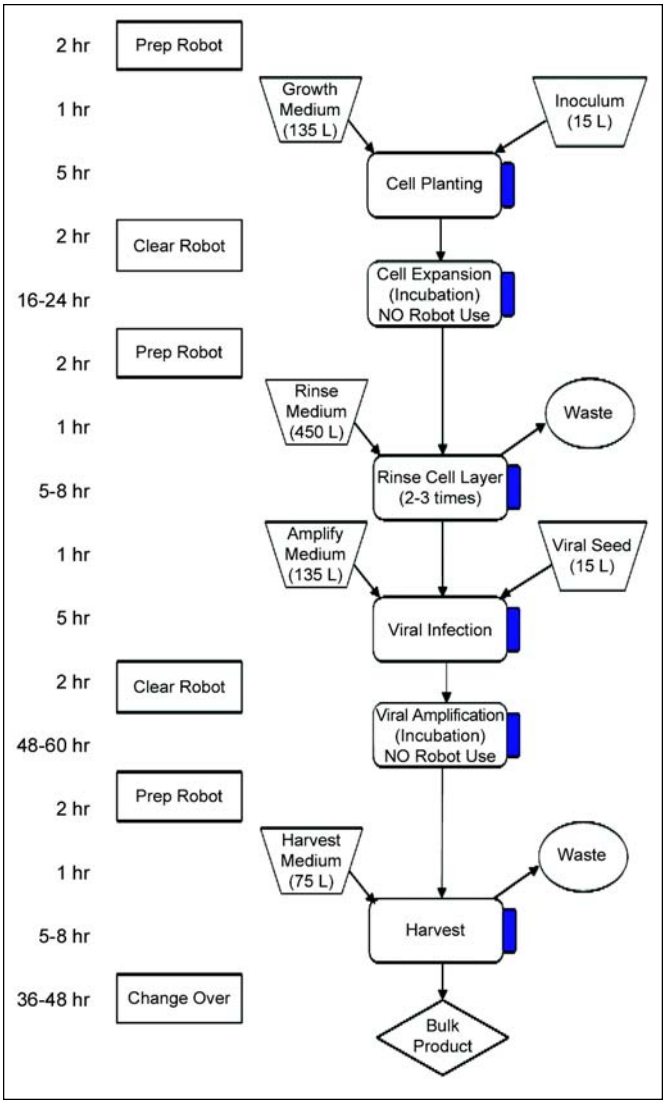

Figure 4. The roller bottle process.[14]

prototype processes. Modern roller bottle systems involve discrete robotic manipulations to inoculate the cell populations into the roller bottles, viral infection of the cell population, and harvesting the product from the roller bottles.

Dutton and Fox[14] reviewed the automated roller bottle operation described below from a Life Cycle Costing (LCC) perspective. They concluded that full automation is marginally uneconomic for pilot scale operation, but clearly economic for full production.

The roller bottle process described was characterized by process steps with variable and often lengthy timeframes - *Figure 4*. Further, the overall process is non-linear. For example, the cell planting step average is 35 seconds/bottle whereas viral infection takes 95 seconds/bottle and this rate mismatch creates incubation bottlenecks and variable product wait times in incubation. Lengthy process times and non-linear time variability is the prime contributor to automated roller bottle module under-utilization and, low OEE.

From Dutton and Fox, it was clear that given the low system OEE observed even greater capital cost payback could be achieved through more consistent equipment use. The suggestion was made that further efficiencies could be gained through a sub-lot protocol, as a means of overcoming the significant equipment wait time associated with cell expansion and viral amplification.

Dynamic simulation was originally undertaken to establish the optimum number of sub-lots to process through a single automated system, and the impact of this on incubator space, the preparation of growth and rinse media, and other upstream and downstream process steps. A system layout was used, modified from Dutton and Fox, to include material handling in the form of input and output roller bottle carts - *Figure 5*. Each cart constituted a batch of roller bottles with a variable number of batches constituting each weekly lot. Based on an uninterrupted lot run of six days with two shifts per day, significant simulated line imbalance was confirmed with viral infection representing the greatest bottleneck.

As one means of simulating greater throughput, a model was run to achieve a production schedule based on the synchronization of planting, infection, and harvesting to the viral infection rate. In this scenario, all bottles were allowed to complete the planting phase and then complete an incubation cycle during the two shifts per day that operators were available. The last bottle planted was to be complete in time for robot change over for viral infection. Maximum throughput under this scenario was determined to be low, at 245 roller bottles per lot, but cell planting, infection, and harvesting wait times also were beneficially low. These short product wait times were found to come at the cost of a low OEE of 14% - *Figure 6a*.

A second simulation was constructed to schedule production without synchronizing on the longest critical process step. In this case, variables optimized were throughput and product wait times, while keeping the critical viral infection process within a time frame that was judged to be acceptable. The simulation was carried out on the basis of a two shift day, and resulted in a throughput of 407 bottles per lot and an automated module OEE of 19%. Product wait times at viral infection were seen to increase, but only slightly.

Further simulation was done to determine the effect of running three instead of two production shifts. This third scenario was run, like the first, with the objective of synchronizing planting, viral infection, and harvesting. Under this

	2 Shifts Synchronized	2 Shifts Optimized	3 Shifts Synchronized	3 Shifts Optimized
OEE (robot cell only)	14%	19%	29%	34%
Throughput (bottles)	245	407	525	703
Avg. product wait time (hrs)				
Cell planting	3	4.68	4.83	4.68
Cell infection	0.62	0.67	0.72	0.77
Cell Harvesting	0.57	0.91	0.57	1.12

Table A. Product wait time.

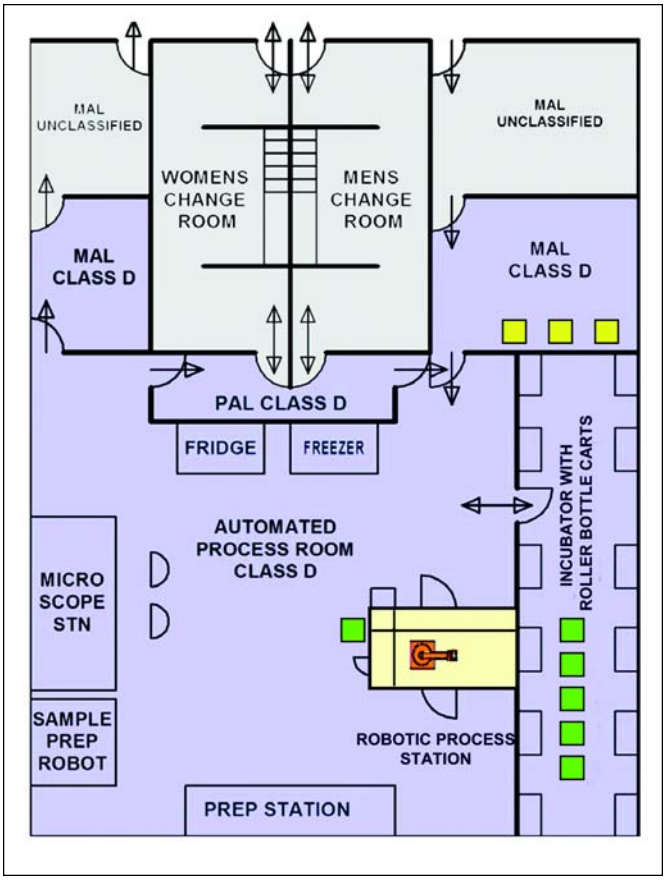

Figure 5. Material handling system layout.[14]

three shift regime, OEE increased further to 29% and throughput increased to 525 bottles, again at a small cost with respect to product wait times.

A final and optimal scenario was run, like the second scenario, to optimize throughput and a reasonable viral infection wait time, and assuming a three shift weekly operation. This resulted in a further increase of OEE and throughput to 34% and 703 bottles respectively - *Figure 6b*.

The optimal scenario came at the expense of a further moderate increase in product wait time - *Table A*. Wait time in this and the other scenarios consists of time for the roller bottle batch or cart to proceed through the incubation and viral infection processes, as well as a second order variability for the same processes relating to each bottle in the batch.

Substituting a conveyorized system for cart-based material handling into and out of incubation would allow the relatively high module OEE to be maintained while decreasing product wait time. Unfortunately, project funding did not allow this hypothesis to be tested through simulation.

Thus, dynamic simulation showed that with the restriction of one robot per automated module, running three shifts more than doubled OEE and throughput with a tolerable increase in product wait time, compared to the base case. Surprisingly, increasing labor by one third was found to increase OEE and throughput by a significantly greater amount, reflecting better production time utilization per shift. Simulation also demonstrated the inefficiency of moving to what seemed at first to be an obvious sub-lot operating protocol, i.e., running smaller sized lots to take advantage of the underutilization of the automated module. Modeling a variety of sub-lot sizes showed that in all cases, and assuming fixed incubation times, the automation becomes a bottleneck with different sub-lots at different stages of processing competing for module time.

Summary

Sophisticated dynamic simulation tools now exist to improve manufacturing efficiency for upstream and downstream discrete manufacturing processes. This article has attempted to demonstrate how these tools can provide valuable insight into process behavior, serve to optimize production, and can mitigate risk in manufacturing design and operation. In this article, as in a previous article,[14] the case is presented for integrating dynamic simulation and financial modeling, particularly lifecycle costing, to facilitate concurrent engineer-

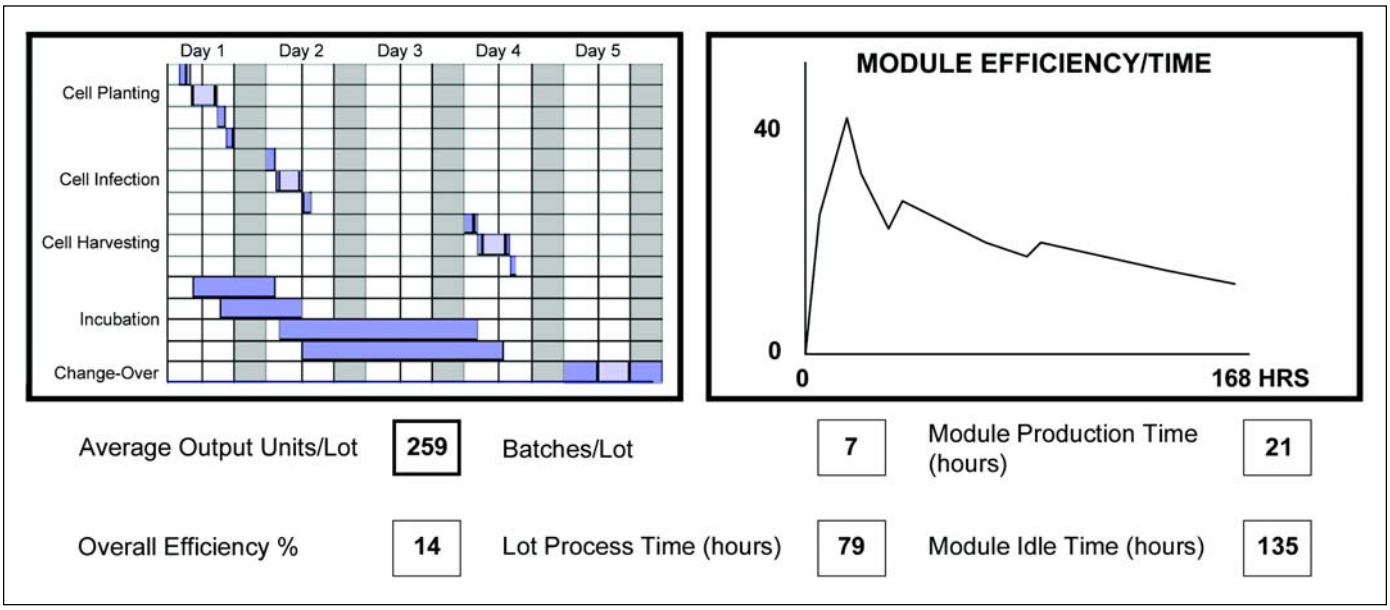

Figure 6a. Roller bottle system – base state.

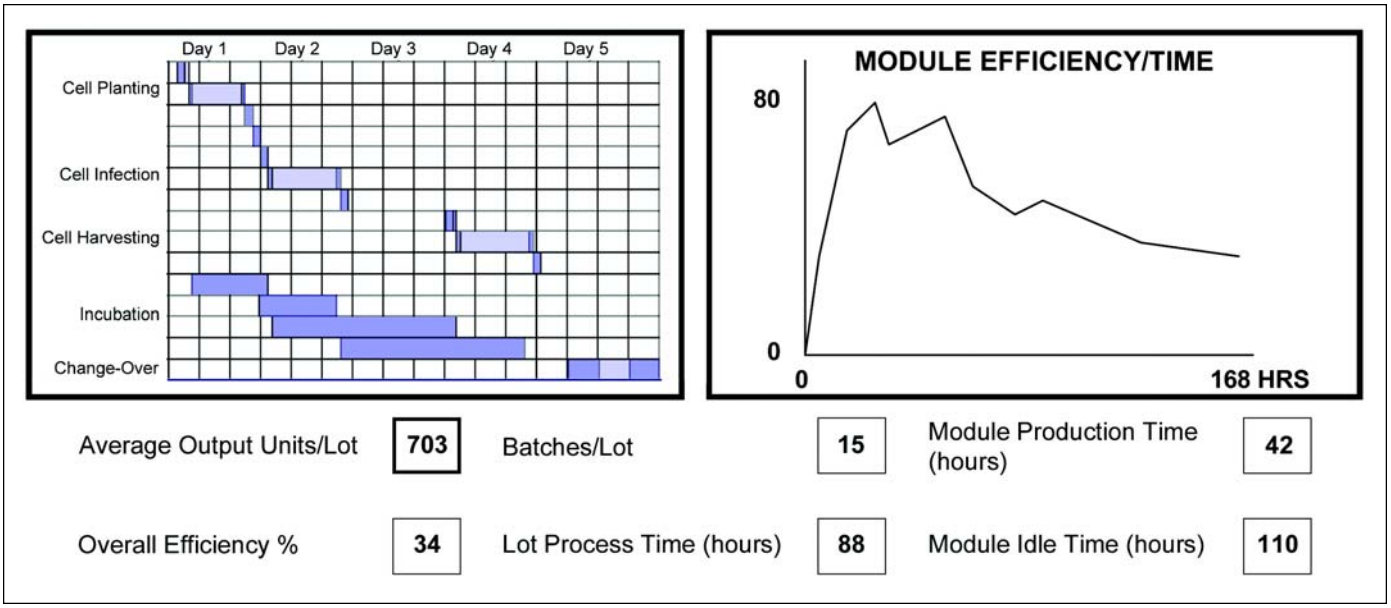

Figure 6b. Roller bottle system – optimized state.

ing of both technical and enterprise-level processes.

A number of challenges stand in the way of using dynamic simulation to facilitate dramatic change.[15] For one, it still takes time to collect the data based on time and motion analysis. Better daily factory discipline in the form of extracting and archiving PLC or SCADA information is desirable, but unfortunately is either not always available or else is costly to obtain through hardware and software "patches." For obvious reasons, it is not advised to use nominal or "as advertised" system parameters.

Another challenge is that simulation and modeling needs to gain greater acceptance within management ranks. It often takes more effort to convince management of the need to invest in simulating a critical process than to develop the model itself. However, simulation practice fits well with what has been said about 21st Century GMPs and greater visibility of simulation practice will diminish this challenge.

Real-time problem solving, or production emulation, is clearly the next step in the use of dynamic simulation. Risk based GMP would certainly be achieved by running a simulation immediately after an incident involving a critical process in order to "instantaneously" decide on remedial action. The means are available, but again discipline (and investment) is required not only to continually extract data, but to continually refine the simulations in question and develop possible alternatives ahead of time.

Many operational decisions in pharmaceutical manufacturing are made purely on prior experience and intuition. Given its utility, we foresee a time when simulation will be mandated for most major capital decisions. Like semiconductor plants, secondary pharmaceutical facilities may be too complex, too costly, and too committed to GMPs – to optimize in any other way.

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ISPE Baseline® Pharmaceutical Engineering Guide for New and Renovated Facilities Volume 6: Biopharmaceutical Manufacturing Facilities – Executive Summary

This executive summary provides an overview of the ISPE Baseline® Guide; Biopharmaceutical Manufacturing Facilities, which applies to products and facilities that house biotechnological processes.

Visit www.ISPE.org for additional information about this Guide and other technical documents available from ISPE.

1 Introduction

1.1 Background

The design, construction, commissioning, and qualification of biopharmaceutical Active Pharmaceutical Ingredient (API) facilities will challenge manufacturers, engineering professionals, and equipment suppliers. These facilities must not only meet cGMP regulations, but must comply with local codes, laws, and regulations. In addition, the technologies employed in operating manufacturing facilities in the twenty-first century will continue to evolve, in areas such as in-line process analytical measurement and control, the use of disposable equipment, enhanced strategies for automation, and alternative methods for protecting the integrity of the product.

The cost of bringing these facilities on line has been rising, in many cases, due to a lack of understanding of regulatory requirements:

- Solutions are applied out of context (approaches for one product are inappropriately applied to a different type of product).
- Product and process are not considered in decisions. A common reason used for decision making is "Company *X* did it so this Company should, as well."
- Confusion regarding required process water quality often leads to process water being over-specified, without economic or scientific justification.

Capital concerns:

- Capital funds may be limited so prudent use of funds is important.
- The need to get quick facility approval at all costs has led to overspending to remove any potential difficulties during inspections.
- Considerable money is spent on non-value added "cosmetic" features, rather than the protection of the product. Money that could have been used for protecting the product is diverted to features with no product impact, such as:
  - mirror finishes, "stainless steel" facilities
  - classified spaces (cleanrooms) where they are not needed, such as for closed processes

1.2 Scope of this Guide

This Guide may be used by the pharmaceutical industry for the design, construction, commissioning, and qualification of new facilities for the manufacture of biopharmaceutical API, also known as Drug Substance. It is neither a standard nor a GMP regulation, nor is it a detailed design guide. It is not intended to replace governing laws, codes, standards, or regulations that apply to facilities of this type. The application of the concepts presented in this Guide for the design of new or renovated facilities is at the discretion of the facility owner or operator. Approaches to meeting GMPs provided in this Guide need not be retroactively applied to currently operating facilities.

This Guide applies to products and facilities that house *biotechnological process*(es). More specifically, it applies to those processes that use cells or organisms that have been generated or modified by recombinant DNA, hybridoma, or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides. Principles outlined in this Guide also may apply to facilities manufacturing other product types, such as proteins and polypeptides iso-

Biopharmaceutical Manufacturing Facilities
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lated from tissues and body fluids. This Guide also applies to facilities dedicated to production of Clinical Trial (CT) materials.

It should be noted that most concepts in this Guide may be applied to allied products, such as blood products and vaccines. Chapter 2 provides further definition of scope and exclusions.

This Guide applies to biopharmaceutical API products, licensed by both the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER).

This Guide fundamentally addresses US GMPs with the GMPs of other countries and regions covered in the Appendices. National Institutes of Health (NIH) requirements and safety issues are mentioned in this Guide where they affect GMPs or design.

- Above all, the reader is reminded that it is ultimately the owner's responsibility to justify decisions and approaches to regulatory authorities.

The audience for this Guide is professionals involved in the design, construction, validation, and operation of biopharmaceutical API manufacturing facilities. This includes regulatory and quality control personnel with a need to understand the technical issues regarding the facility or process:

- The mission of the ISPE Baseline® Guides is to help operating companies satisfy the GMPs and produce product in a manner that allows the manufacturer to stay in business.
- This Guide should not be used as a GMP; instead it focuses on the use of resources to meet GMP.
- By its nature, this Guide cannot be comprehensive, but offers a structured approach to satisfying the intent of the GMPs. If an issue is not covered in this Guide, or if alternatives appear feasible, the reader is advised to discuss them with the appropriate regulatory authorities before making any significant financial commitments.

- This Guide does not attempt to cover biopharmaceutical GMPs that do not address the facility or the manufacturing process technology.

1.3 Key Concepts of this Guide

1.3.1 Does the Process Equal Product?

There is a continuum of process and facility approaches based on the product and processes used to make the product. The best engineering solution makes optimal use of people, materials, and capital, while protecting the product. There is no single "right" or "perfect" way to design and operate the facility. The design of a facility, however, has a profound impact on the process design and on how the facility is operated.

Due to historical limitations in analytical methodologies and an incomplete understanding of the relationships between process variables and final product quality, biopharmaceutical processes have, historically, been viewed as "black boxes." Thus, there has been a prevailing view that the "process equals the product;" because there was a risk that changes in the process could result in unexpected or unintended consequences that could not be detected. This view, coupled with a lack of process data to predict the effects of change, has led to a reluctance to alter biopharmaceutical processes, a reluctance that has been reinforced by conservative regulatory approaches. Manufacturers were challenged to assure that product identity remained consistent, that changes in the API would be identified, and that any changes would not affect the safety or efficacy of the final product.

These historical limitations posed two very important questions:

- How could a manufacturer assure the identity of the final product in the case of process variations?
- How could a manufacturer assure the final product's quality and consistency with changes in scale or changes in the facilities of manufacture?

Fortunately, as the industry has developed a better understanding of biopharmaceutical processes and as analytical methods have improved, a better understanding of the "cause and effect" relationship between process variables and products has evolved. This evolution has caused a change in focus to those issues that are critical to the consistent manufacture of high quality products. Products and processes have been proven to be transportable between facilities and can be operated on different scales with sufficient understanding of the process to help manage process duplication and scale up.

1.3.2 Process Design is tied to Facility Design

This Guide considers the variables that most directly affect the process and facility. These are discussed extensively in Chapter 3 and Chapter 6, including:

- Open versus closed processing:
  - Closed processing places emphasis on physically segregating the product from the environment.
  - Open processing places an emphasis on the operation of the facility and its personnel.
- What works best for one product, facility, or process scale may not work best for another product, facility, or process scale.
- Features that work well in a single product facility may be inadequate for a multiple product facility.
- Process controls:
  - Automation is not a GMP requirement, but if automation is used, there are GMP implications. Chapter 7 provides further insight with regard to automation.

For subjects generic to all pharmaceutical facilities, the reader is directed to other sources for further in-depth information.

- The basics of Qualification are covered in the ISPE Baseline® Guide on Commissioning and Qualification.
  - Commission everything in accordance with Good Engineering Practice, but qualify only "Direct Impact" systems and critical components of those systems.
  - Design Qualification or Enhanced Design Review will assist in achieving compliance with ICH Q7A.
  - Qualification considerations specific to biopharmaceutical systems are considered in Chapter 8 with reference to topic-specific qualification activities provided in Chapters 3 through 7.
- Water and steam systems are considered in the ISPE Baseline® Guide on Water and Steam Systems.

The Guide user is encouraged to work with the regulatory authorities to resolve unique issues before they result in inappropriate or ineffective design decisions.

1.3.3 Controlled Processing

The product must be protected by controlling the process, and often, its surroundings. This requires knowledge of the product and process, and protection utilizing segregation and flow patterns. Chapter 3 discusses controlled processing in more detail.

1.3.3.1 Know the Product (and Its Process)

Intimate knowledge of the product, its specifications, the processes involved, and processing variables is essential. Evaluation of potential contamination routes is needed. Data that demonstrate control of the process and to justify processing decisions will be key to a successful facility.

1.3.3.2 The Process Should Not Add Contamination

The contamination profile of the process must be known and the process must be controlled to specifications.

- Process water requirements should be based on the purity requirements of the product and may vary, depending on product purity at the stage of the process in which it is used (see Chapter 5).
- Chapter 3 discusses recovery from upsets and prevention of contamination during manufacturing operations.

1.3.3.3 Contamination Control Strategy

Chapter 2 introduces the concept of a 'Product Protection Control Strategy' and describes its essential elements, taking into consideration both the API and the final pharmaceutical specifications. Bulk biopharmaceutical manufacturing operations are based on controlling bioburden in the product (see Chapter 3). Aseptic-like processing steps or "sterile" processing operations using sterilized process equipment are usually operated as closed systems.

Chapter 3 also highlights housekeeping, cleaning, and fumigation. Chapter 4 discusses equipment cleanability and closure.

1.3.4 Segregation and Flow

Segregation protects the product from contamination from its surroundings (i.e., from the facility and other products). Flow patterns in the facility influence segregation, especially where more than one product is manufactured. Chapter 6 provides more detail to help decision-making regarding segregation and flow.

1.3.4.1 Primary and Secondary Segregation

The concept of "segregation" reflects a need for the design to protect the product from contamination as it progresses through a series of unit operations. The avenues to accomplish segregation include, among others, procedural, physical, environmental, and chronological (temporal) separation.

A segregation method or strategy that addresses a direct environmental contamination threat to the product is termed primary segregation. Primary segregation concepts define the basic organization of the biopharmaceutical plant design and establish environmentally controlled envelopes around specific open steps of the process.

A segregation method or strategy that addresses the product in a protected state (such as in a sealed enclosure), and mainly addresses reducing potential mix-ups in the facility and opportunities for human error, is referred to as secondary segregation. Secondary segregation is generally applied to reinforce procedural control of areas, activities, and personnel, but is usually applied in instances where supporting components, equipment, or product are closed and adequately protected from the surrounding environment. Such secondary separation mechanisms can vary widely and include physical, procedural, or chronological controls.

Whereas primary segregation affects the immediate quality of the process, secondary segregation measures are traditionally implemented to minimize the potential for human error. Protection of product may be accomplished through a combination of primary and secondary segregation (see Chapters 2, 3, and 6).

1.3.4.2 Flow and Traffic Patterns in the Facility

Implementation of the segregation strategies results in "flow:"

- Flow patterns should address scale, volume, and duration of expected traffic.
- Flow patterns also should address upset conditions (such as maintenance and change out of large equipment) and future construction.
- A carefully planned materials handling philosophy must be defined before establishing flow patterns.

The design of the flow patterns should be based on the requirements or needs for primary and secondary segregation. Critical Flow Patterns include:

- materials flow
- product flow, including intermediates and hold points
- personnel flow
- equipment flow (through cleaning protocols)
- waste flow

To minimize the risk of product contamination and maintain cleanliness, flow patterns can dictate certain design details, such as:

- materials of construction and architectural finishes
- building layout and area air classifications (eliminating contamination pathways via air, people, or equipment)
- cleaning of equipment and piping strategies:
  - use of Clean-In-Place (CIP) (see Chapter 14 - Glossary)
  - use of Steam-In-Place (SIP) (see Chapter 14 - Glossary)
  - location and operation of equipment wash facilities

1.3.5 Open versus Closed Processing

If a unit operation is demonstrated closed, it may operate in Controlled Non-Classified (CNC) space. Some closed final bulk processing may require classified space (see Chapter 6).

- Closed: refers to segregation by physical means (equipment) to protect the product and process from contamination by the surrounding environment (outside the equipment). The measurements used to determine the condition of being closed ("closure"), which is defined by the owner, must be sufficiently stringent to prevent contamination of the product.
- Different operating systems have varying degrees of closure based on process requirements. The closure of some systems may be absolute, while others provide a lesser degree of segregation. Controlled Non-Classified (CNC) space should be reserved for the processes that can be verified as being closed. The facility design should incorporate measures/protection when the affected systems may be momentarily "opened" during operations.
- The use of a "rigid" definition may limit the understanding of "closed."

If a process cannot be proven to be closed, it must be considered to be open (see Chapter 14 - Glossary). If a unit operation is open, the product is normally protected in a controlled classified space.

Most facilities will require a combination of both classified space and controlled non-classified environments.

Both classified and CNC spaces require some type of routine ongoing quality assessment to confirm that the space is under control and that the intended level of quality consistently prevails. The environmental assessment technique used, as well as the overall intensity and frequency of assessment, depends on the criticality and characteristics of the operations carried out within that space. CNC spaces do not require "classic" environmental monitoring.

The choice between closed processing in CNC space and open processing in a classified space is often determined by the scale of the process, the cost of operations, and the value of the product at risk.

Chapter 4 provides information to help in selecting process equipment to meet open or closed requirements. Chapter 6 discusses the effects of process closure on the facility.

1.3.6 Scale Affects Decisions

Chapters 3, 4, and 5 deal with process design and support utility design issues connected with process scale, and Chapter 6 covers facility layout options.

One size does not fit all. As the scale of the process increases, there is a shift toward:

- vertical layouts with gravity flow of materials
- more closed operations
- more primary segregation
- equipment fixed in place (often dedicated)
- more automation
- CNC space instead of classified space (due to closed processing)

Small process scales tend to include:

- horizontal process flow
- open operations
- segregation by time (e.g., campaigning)
- manual operations (mixing, etc.)
- less automation
- more portable equipment, often shared with other products
- more need for classified spaces

1.3.7 Single Product versus Multiple Products Manufacture

As will be covered in Chapter 3, when more than one product is manufactured in a facility, ensuring the safety and quality of a product becomes more difficult. Multi-product manufacturing facilities may segregate products by campaigning (one product at a time) or may process multiple products concurrently.

- Campaigning relies heavily on validated cleaning and changeover procedures (see Chapter 3).
- Concurrent manufacturing must avoid cross-contamination through physical segregation and operating procedures (see Chapter 3 and Chapter 6).

1.4 Using this Guide

1.4.1 Organization of this Guide

In addition to the table of contents, an overview of the Guide's structure is shown in Figure 1-1. The arrows represent the intended flow of information when the Guide is used to define a facility project.

1.4.2 Application of this Guide

It is important to approach a facility project in the proper sequence. As shown in Figure 1-1, it is necessary for the facility designer to first understand the GMP requirements (see Chapter 2 and Chapter 9 - Appendix) and then address the product and operational requirements (see Chapter 3). From there, once operational concepts have been established, User Requirements defined, and perhaps even a Functional Design created, the discipline designers may begin detail design. It is impractical to begin facility design or to make a commissioning and qualification plan without first understanding the basics (see Chapter 2 and Chapter 3).

Users of this Guide are advised to refer to other ISPE Baseline® Guides for more detailed or complementary information. For example, water and steam systems are thoroughly discussed in the ISPE Baseline® Guide on Water and Steam Systems, and the design of classified pharmaceutical manufacturing space is discussed at length in the ISPE Baseline® Guide on Sterile Manufacturing Facilities.

Users of this Guide also are encouraged to understand thoroughly GMP and specific product requirements, before attempting facility design. Where there is conflict or a lack of understanding, manufacturers and engineers are encouraged to discuss concepts with the appropriate regulatory agency. Such early discussion opens dialogue and facilitates a common understanding of the significant regulatory concerns for a specific manufacturing scenario, prior to construction.

2 Interpretation of the Regulatory Basis for Facility Requirements

During the design of new facilities, every manufacturer faces numerous issues that may significantly affect the facility cost. These include process defi-

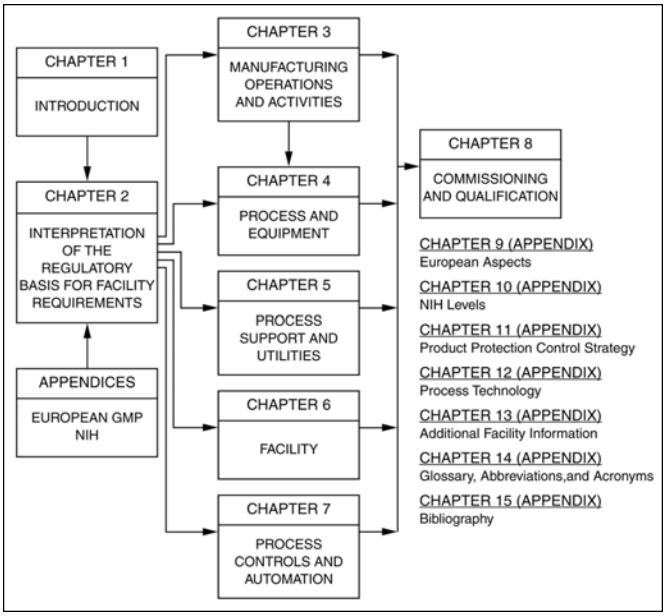

Figure1-1. Overview of the Structure of the ISPE Baseline® Guide on Biopharmaceutical Manufacturing Facilities.

nition, process equipment requirements, multiple products (e.g., production of a single versus multiple products, campaign versus dedicated production), and the definition of a suitable manufacturing environmental quality to support manufacturing, water requirements, and facility layout. While some of the issues faced may affect the quality of the Active Pharmaceutical Ingredient (API or bulk drug substance), others may have no impact.

The evolution of facilities for manufacturing biopharmaceutical products has led to many extremes in size, complexity, and capital/resources. Processing approaches and designs suitable for a small-scale process are often inadequate or inappropriate for a large-scale facility. The multi-product facility will differ in certain key areas from either of these dedicated facilities.

The primary element to be considered in a facility manufacturing a bulk biopharmaceutical drug substance is the ability of the facility and the process to protect the API, i.e., to prevent contamination. One mechanism by which product protection issues may be addressed is through an optional document called the Product Protection Control Strategy (PPCS). Specifically, each company should determine the appropriate requirements to provide adequate protection for its product(s), and thereby, the requirements for the completed facility. No single solution or design fits all drug substances or products since the decisions made and incorporated in the facility will depend on the following:

- nature of the process and product (i.e., contamination-sensitive processes to less sensitive processes, open versus closed processing, etc.)
- scale and complexity of the process
- number and types of the products in the facility

This Chapter addresses some of the significant process-related concepts and facility attributes with regulatory implications to be considered when designing and operating a facility. Key points include:

- A single, universal "GMP" standard or approach to biopharmaceutical facility and process design does not exist. The nature of the product and its processes greatly influences decisions based on the appropriate interpretation of the relevant GMP.
- Biopharmaceutical manufacturing operations are not usually intended to produce a sterile drug substance, but rather one of low bioburden. Although the adoption of aseptic manufacturing techniques and facility standards has occurred in the industry, such standards are not generally mandatory, except where the final API bulk product is required to be sterile and pyrogen free. Where controls are required by the process to prevent microbial contamination to certain specific steps, e.g., fermentation, cell culture, purification steps susceptible to microbial contamination, aseptic standards should be properly applied. The production process and facility should include the appropriate controls to prevent, limit, and detect API contamination.
- Processes may be closed or open. Closed processing presents less risk to the product and presents fewer demands on the facility design. Local protection should be used with open processes to prevent contamination of the product.
- Multiple products, segregated by appropriate procedural or physical means, may be produced within a single facility.
- Water used in manufacture should be appropriate to the process; WFI is sometimes used throughout the process, but may not be necessary for every production stage.

3 Manufacturing Operations and Activities

This Chapter covers the operational aspects of a biopharmaceutical facility, as opposed to the physical design of the facility itself, and addresses key regulatory issues and concepts defined in Chapter 2. The Chapter addresses the impact of facility and equipment design decisions on manufacturing operations. Conversely, the Chapter also describes how operability and maintainability considerations should influence the design of a biopharmaceutical facility. Consideration also is given to production management, process operators, and other plant support personnel are included. Important concepts addressed in this Chapter are as follows:

- **Operational and Procedural Controls** can play an important role in assuring the quality of the product, and must be factored into the "open versus closed" design decision. Application of these types of controls with a well-trained manufacturing staff can often help to minimize costly over-engineered systems.
- **"Bioburden-Controlled Processing" and "Pyrogen (Endotoxin)-Controlled Processing"** are key operational concepts that have a significant impact on process and facility design, and both are distinct from sterile processing. Some features of traditional sterile design and operation may be employed, but are typically not required to establish the appropriate level of control.
- **Segregation** is critical in any biopharmaceutical operation to ensure product protection. Traditional applications include the following:
  - between organisms, products, or technologies
  - between processing steps (e.g., upstream and downstream operations)
  - between raw materials or products at various stages of quality control or process step
  - between components or equipment at different stages of cleanliness

Segregation can be accomplished by "primary segregation" (physical), "secondary segregation" (chronological or procedural), environmental control (pressure cascade), or process design (system closure).

- In a **Multi-Product Operation,** products can be either campaigned

or processed concurrently. For campaigned products, the focus is on cleaning validation, changeover procedures between products, and line clearance procedures. For concurrent product manufacture, the focus is on segregation, procedural controls, and avoidance of cross-contamination. In all cases, the overall guiding principle is to ensure the quality and safety of the product.

- **Viral Clearance (Reduction and Inactivation):** biopharmaceutical processes commonly use raw materials from biological sources, especially animal sources, starting with the cell line and often extending to supplements added during the cell culture and purification stages. Cell lines used in the biopharmaceutical industry are extensively characterized for identity, safety, and purity, and are tested for the presence of infectious agents. However, mammalian cells are capable of harboring and amplifying viral contamination, and manufacturers using mammalian cells must demonstrate adequate viral clearance. In addition, increasing concern over the transmission of prions from animal-sourced raw materials has prompted manufacturers to take additional measures to minimize the risk of such contamination. The decision on how/where to accomplish viral clearance can have an impact on the equipment design, and may affect the design and layout of the facility.
- **Manufacturing at different stages of product development** is important for many biopharmaceutical companies, particularly those facing their first major capital investment in manufacturing facilities. While the regulations are clear in stating that GMP compliance is required for all stages of clinical development, it is also recognized that, in most cases, the manufacturing process is not completely defined during early-stage clinical work. It is important that process issues having significant impact on the facility design are identified as early as possible. During early-stage clinical manufacturing, the focus of process/facility design and validation should be upon areas that have the greatest impact on product quality and consistency.
- **Operating and maintenance procedures** also should address potential process upsets. Cleaning and housekeeping will be facilitated by adequate working space. Cleaning of Controlled Non-Classified (CNC) areas requires only potable water, but increasing control and purity may be needed for classified spaces.

4 Process and Equipment

This Chapter is primarily concerned with design aspects of biopharmaceutical processes and equipment. Specifically, this Chapter deals with the design of biopharmaceutical process equipment, and associated piping and instrumentation, which contact a product or its components at a stage in the process where such contact could influence the quality, safety, purity, strength, or identity of the ultimate product. The primary audience for this Chapter is process and equipment engineers. This Chapter is not intended to be a comprehensive design guide, but does include a number of issues which should be considered in process and equipment design.

In general, biopharmaceutical processes are similar in that nearly all have fermentation/cell culture production steps, harvest steps, purification steps, formulation steps, and final bulk filling steps. Although manufacturing processes may differ, certain critical process variables are consistent from product to product, and certain key considerations for each processing step apply to all processes.

Within each process step, there are process considerations driven by the overall philosophy of the organization operating the process. The design approach that is chosen based on these considerations (GMP and business drivers) will result in a set of criteria to be used for both equipment selection and overall facility design. There is no single answer to the majority of the process considerations mentioned; however, the combinations of the choices and solutions will define reasonable, compliant process designs.

Various types of equipment share similar design considerations and requirements. Specifically, cleanability/drainability, surface finish, materials of construction, shear generation, closure level, containment level, and pressure/temperature requirements must be considered for virtually any piece of equipment or device used in biopharmaceutical manufacturing. Improper consideration can lead to processing systems that are either not operable (placing product at risk) or are operationally inefficient (lower process yields). Key topics addressed in this Chapter include:

- **Typical Biopharmaceutical Processes:** simplified process flow diagrams of several typical biopharmaceutical processes are presented.
- **Critical Process Variables:** key processing attributes (critical variables) for various processing steps are identified for typical unit operations. Critical process variables, such as temperature, pH, conductivity, bioburden, endotoxin, product concentration, by-product levels, purity, and stability, are generally similar from process to process. However, the product specifications, acceptance criteria, implications, and applicable design options from process to process may vary significantly.
- **General Considerations for Equipment Design:** equipment design considerations are common to most biopharmaceutical unit operations.

General equipment considerations, such as materials of construction, cleanability, avoiding cross contamination, open versus closed, process monitoring, safety, containment, and maintenance, can be applied to most process equipment, and design considerations are outlined. Similarly, there are design considerations applying specifically to particular areas, such as cell culture and purification. These are outlined in the form of checklists for the process and equipment engineer:

- **Specific Equipment Design Considerations:** design considerations that are unique to specific biopharmaceutical process equipment types.
- Although a detailed analysis of every unit operation used in biopharmaceutical processes are outside the scope of this Guide, unit operations generally fall within the broad process operation areas:
  - Raw Material Storage/Handling
  - Weigh/Dispense
  - Media/Buffer/Component Preparation/Hold
  - Inoculum Preparation
  - Fermentation/Cell Culture
  - Recovery/Harvest
  - Purification (including Column Packing)
  - Bulk Filling
  - CIP
  - SIP
  - Biowaste Deactivation

Specific design issues affecting unit operations in these areas are outlined in this Chapter.

5 Process Support and Utilities

This Chapter provides guidance in design and operation of utility services supporting the manufacturing of biopharmaceutical products. Utility systems addressed in the Chapter include:

- Pharmaceutical Water Systems
- Cleaning, Sterilization, and Depyrogenation Systems
- Process and Utility Gases
- Process Temperature Control Systems
- Bio-Waste and Process Waste Handling
- Seal Support Systems
- Plumbing and Piping Systems
- Emergency Power

This Chapter focuses on process support systems that affect the ability to meet GMP production requirements and identifies the major GMP issues for each of the systems addressed. Guidance is provided on the design of systems to minimize the risks of product contamination or unreliable production.

For purposes of qualification and commissioning, this Chapter categorizes process support utilities as having "Direct Impact," "Indirect Impact," or "No Impact" on the product. This Chapter recommends full qualification and commissioning of "Direct Impact" systems. Systems with "Indirect Impact" or "No Impact" should be commissioned consistent with Good Engineering Practice. Key concepts discussed in this Chapter are:

- Process support system features that affect GMP ("Direct Impact" systems and the interfaces that separate them from other systems) are identified, and vulnerable characteristics are explained.
- Methods to minimize product contamination risks from process support utility systems are presented.
- Except when required for safety or operational reasons, system design should minimize the need to service and otherwise access process support systems from within production areas.
- Systems that might enable transmission of contaminants are identified with methods for prevention provided.
- Methods to define commissioning and qualification requirements for process support utilities are presented.
- A summary of key concepts for biopharmaceutical water systems is provided.

6 Facility

Biopharmaceutical manufacturing facilities may be very complex and result from projects that focus on the attributes of the product(s) being produced, the attributes of the process, and the attributes of the facility that meet cGMP guidelines. The facility design team should become familiar with the topics discussed in this Chapter to understand how each will affect the final facility design and operation.

This Chapter reviews:

- the impacts of process and unit operations on facility design
- how product attributes play a key role in defining facility design
- the importance of adjacencies in defining operational flow to minimize potential contamination opportunities
- the impacts of containment and closed processing on facility design
- the definition of area environments and their impact on facility layout and design
- the issues related to single product versus multi product production philosophy
- air lock and gowning room alternatives
- considerations for effective process and production support areas
- regulatory considerations in facility design
- layout alternatives, such as the practicality of vertical flow
- finishes (these are considered in other ISPE Baseline® Guides with references provided in this Chapter)
- discretionary (non-GMP) considerations

7 Process Controls and Automation

This Chapter provides points to consider when developing instrumentation and automation strategies for biopharmaceutical operations. This process starts by determining the details of the biological process to be controlled:

- What are the critical operating conditions?
- What can adversely affect the process or product?

Once the process and critical operating parameters are identified, the optimal level of automation versus control via manual procedures can be determined.

Automation is not a GMP requirement; however, when automation is used, it carries with it GMP requirements. If properly applied and validated, automation can help achieve ongoing GMP compliance. When not properly managed and designed, automation can result in problems with

project schedule and cost.

Topics covered in this Chapter are organized as follows:

- biopharmaceutical automation issues
- appropriate level of automation
- The following biopharmaceutical unit operations are specifically discussed in this Chapter:
  - Fermentation/Cell Culture
  - Chromatography
  - SIP
  - CIP
- control system maintenance
- validation of automation systems

The intended primary audience for this Chapter includes:

- Instrumentation and Control Engineers
- Process Engineers
- Information System or Technology Specialists
- Production Operations Staff and Management
- Process Development Scientists
- Validation Engineers

8 Commissioning and Qualification

A biopharmaceutical manufacturing facility is commissioned and qualified in the same manner as any other pharmaceutical manufacturing facility. Many aspects of the qualification of aseptic manufacturing facilities apply to classified spaces in biopharmaceutical facilities although there are many areas that require only commissioning in accordance with Good Engineering Practice.

It is imperative that, before detail design begins, the owner and engineers develop User Requirements Specifications and Functional Design Specifications. These activities will identify product/process critical parameters and their acceptance criteria (forward processing criteria), against which post-construction qualification will verify performance of the "Direct Impact" systems that are identified in the Functional Design.

The ISPE Baseline® Guide on Commissioning and Qualification provides guidance in identifying the systems needing qualification. A few highlights are provided here, but the facility engineer is directed to the ISPE Baseline® Guide on Commissioning and Qualification for further information.

9 Appendix – European Aspects

The purpose of this Appendix is to highlight the general requirements in Europe and to point out the differences between Europe and the US.

Although the general trend is to harmonize regulatory requirements worldwide, driven by organizations like the ICH, differences continue to exist. Within Europe, the EU directives are assisting in the harmonization of general requirements, by providing the minimum standards. The national laws need to comply with these standards, but are allowed to be more stringent.

10 Appendix – NIH Levels

This Appendix provides a listing of National Institutes of Health (NIH) requirements and safety issues, where they affect GMPs or design.

11 Appendix – Product Protection Control Strategy

The elements in a typical Product Protection Control Strategy (PPCS) are listed, suggesting information that might be included in a PPCS.

12 Appendix – Process Technology

Increasingly, the biopharmaceutical industry is integrating single-use products into the process flow. This Appendix briefly reviews some of the key features and components of typical disposable containers with general considerations, both positive and negative, in various applications in biopharmaceutical processing.

13 Appendix – Additional Facility Information

The information presented in this Appendix provides more detail for designers to consider in meeting the GMP concepts considered in Chapter 6.

14 Glossary, Abbreviations, and Acronyms

A glossary of pharmaceutical industry terminology relevant to this Guide.

15 Bibliography

A list of publications referenced by the Guide and which provide further reading on the topic of this Guide.

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The ISPE Facilities Technical Documents Subcommittee Wants Your Feedback

Over recent years the importance of energy efficiency and sustainability has become more prominent within the design community. Mainstream design practice within the commercial sector is well into the transition to incorporate sustainable design. But while many of us have made great strides within our own companies, the overall movement in the pharmaceutical industry is still in its infancy.

From an outsider's perspective, this must seem odd. We pride ourselves on our contributions to life. And, no matter where our personal contributions lie, we take pride in the fact that we are contributing to a better world. ISPE is an organization which, at its core, is concerned with human well being and is continuously working to improve the quality of life for all. Bearing that in mind, it seems appropriate for ISPE to lead the way in transforming pharmaceutical industry practices to better incorporate sustainable design principles.

Applying environmentally sustainable and energy efficient concepts in a highly regulated industry is challenging. We believe those challenges may merit the formation of a new initiative within ISPE – an initiative focused on helping pharmaceutical manufacturers better understand how and when sustainable design features can be integrated into their facilities and processes.

We believe an initial step may be to establish a forum for the exchange of information and ideas related to sustainable design of pharmaceutical operations between ISPE members, but we need your input on the following:

- Is this issue worth the investment of ISPE's resources, most of which will be provided by volunteers who will dedicate time and energy to this effort?
- Do you have ideas for how to best approach this?
- Would you or your company be willing and able to support this effort?
- Are you interested in participating?

If you'd like to know more about becoming involved,
would like specific information about the goals or objectives of this
initiative, or provide your feedback on the questions above,
please e-mail **Guides@ISPE.org**.

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BE&K Building Group to Build Orlando Facility for Burnham Institute for Medical Research

The BE&K Building Group has been awarded a $55 million contract from Lake Nona Property Holdings, LLC to provide preconstruction and construction management for the Burnham Institute for Medical Research's East Coast Research Facility to be located in Orlando, Florida, USA. Headquarted in La Jolla, California, USA, the Burnham Institute for Medical Research is a 30-year-old independent institution that has contributed to the development of new drugs for Alzheimer's disease, heart disease, and cancer. Construction is expected to start in October 2007 with an anticipated March 2009 completion.

BE&K Building Group, Inc., www.bekbuildinggroup.com.

Peristaltic Pumps

Watson-Marlow Bredel's newest brochure features information on the company's line of pumps and tubing products designed for the pharmaceutical and biotech industries. Perfect for dispensing delicate, viscous, corrosive, or abrasive fluids in research and production processes, these pumps are ideal for filtration, fermentation, disposable bioprocesses, and dispensing applications, and meet full quality testing standards, including USP Class VI, ISO 10993, and USDA requirements.

Watson-Marlow Bredel, www.watson-marlow.com.

Auger Feeder

Schenck AccuRate's new PureFeed® AP-300 pharmaceutical auger feeder feature an FDA-compliant EPDM feedhopper that is disposable and recyclable. This allows for simpler, shorter cleaning cycles with virtually no chance of cross contamination when moving from one material to another. The durable construction of the hopper provides the option of reuse if disposal is not preferred.

Schenck AccuRate, www.accuratefeeders.com.

Filter Dryer

The Powder Systems Limited small scale contained filter dryer provides maximum efficiency and versatility in R&D kilo labs. This lab scale system has a 0.05 m2 filtration area with 15L liquid capacity and typical 2 to 8L wet cake capacity. This small mobile filter dryer is ideal for API chemical kilo labs requiring a solution for filtration and drying of slurry from multiple reactors of various sizes, as is typical in R&D facilities.

Powder Systems Limited, www.powdersystems.com.

Contract Filling Service

Rommelag not only specializes in blow/fill/seal machines, but offers a contract filling service through its subsidiary companies Holopack in Germany, Holopack International in the USA, and Maropack in Switzerland. Everyday these subsidiaries manufacture several million containers for customers from all over the world. Rommelag develops a wide range of packaging solutions using its in-house systems to meet customers' requirements.

Rommelag, www.rommelag.com.

Filter Module

Camfil Farr's new "RFM22" ducted terminal filter module delivers leak-free protection for ISO Class 5 - 8 applications in the pharmaceutical and biotech industries. The all-welded module incorporates a gel seal HEPA or ULPA filter and is designed specifically for use where hoods must be regularly validated for performance and leak-free operation.

Camfil Farr, www.camfilfarr.info.

Silicone Tubing

AdvantaPure's new silicone tubing, APSPG, is designed for the unique demands of peristaltic pumps. APSPG is made to withstand repeated compression and release for consistent, dependable performance. It is ideally suited for pharmaceutical, biomedical, biotech, chemical, laboratory, and R&D applications.

AdvantaPure, www.advantapure.com.

Dust Collector

Farr Air Pollution Control's popular "GOLD SERIES®" dust collector offers a new high performance explosion vent for applications involving the capture of explosive dusts. The new "X-vent" is manufactured in accordance with NFPA standards and carries CE and ATEX certifications. The multi-ribbed vent delivers a very high negative static operating pressure rating of -80" WC for enhanced performance, and is designed to open up at +1 psi (30" WC).

Farr Air Pollution Control, www.farrapc.com.

Process Controller

Honeywell's Experion® Process Knowledge System (PKS) C300 Process Controller has achieved the new Mu Security Industrial Control Certification (MUSIC). The MUSIC certification is designed specifically for IP-based controllers and is closely aligned with the emerging ISA-SP99 security standards. It enables organizations that rely on critical infrastructure or process control to ensure their network equipment and applications meet industry-defined benchmarks for safety, robustness, resiliency, and conformance.

Honeywell International, www.honeywell.com.

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Facility of the Year Awards Recognize Smart Building

Submission deadline for 2008 Program is 30 November 2007

While cost constraints continue to force the pharmaceutical industry to downsize, it is also a main driver for new and creative thinking when constructing or renovating a facility.

The industry's fast-changing focus from building bigger to building smarter is a reality recognized by the Facility of the Year Awards (FOYA) program, sponsored by ISPE, INTERPHEX, and *Pharmaceutical Processing* magazine.

"You don't have to have an *Architectural Digest* shell to capture our attention," said Andy Skibo, 2007 FOYA Judging Panel Chair and Vice President Corporate Engineering and Capital Projects for Amgen.

According to FOYA judges, it's the innovative and efficient use of space within the shell that matters.

Now in its fourth year, the Facility of the Year Awards program recognizes pharmaceutical manufacturing projects that utilize new applications of technology and cutting-edge approaches in facility design, construction, and operation to reduce the cost of producing high quality medicines.

Some examples of cutting-edge approaches in the 2007 submissions include use of disposable technologies, modular design, automation, process design flexibility, and creative project delivery.

The high-profile program is now accepting submissions for the 2008 competition. The submission deadline is 30 November 2007. The newly enhanced program recognizes projects that demonstrate excellence in the following categories:

- Process Innovation
- Project Execution
- Equipment Innovation
- Facility Integration
- Project Execution Regional Excellence

The overall winner, selected among the five Category Winners, will be announced at ISPE's Annual Meeting in October 2008 in Boca Raton, Florida, USA. Prior to the announcement, Category Winners will be introduced during INTERPHEX2008 in Philadelphia, Pennsylvania, USA. *Pharmaceutical Engineering* and *Pharmaceutical Processing* magazines will provide extensive coverage throughout the year.

Global manufacturing facilities are encouraged to apply. Since its inception, the program has attracted submissions from more than 20 countries, including Belgium, Canada, China, Denmark, Germany, Ireland, Japan, the United States of America, and the United Kingdom.

The program generates opportunities for winning manufacturers and their key supporting organizations to showcase their ingenuity and motivate their colleagues through the sharing of best practices. "This is a challenging time to be in our business," said Skibo. "But these challenges make it the most exciting time to be in our business, requiring a lot of creativity and closer teamwork."

Program participation has been made easier with the addition of an on-line submission process. Companies are now able to download simplified forms for completion and upload them to a secure site for judging.

For complete information about the Awards program and submission procedures, as well as to download the on-line application forms, visit www.facilityoftheyear.org. Specific questions can be addressed to Scott Ludlum, ISPE Director of Business Initiatives, by tel: +1-813-739-2284 or by e-mail: sludlum@ispe.org. The on-line submission form can be accessed at www.facilityoftheyear.org. PE

Amsterdam Conference: Containment, Packaging, HVAC, API, and More

ISPE will play host to experts and worldwide regulators who will present current trends, challenges, and practical solutions at the Amsterdam Conference 26-29 November 2007, at the NH Grand Hotel Krasnapolsky, Amsterdam, The Netherlands. The conference will provide the opportunity to meet face-to-face with industry experts and worldwide regulators.

Topics will include:

- **Containment Technology Forum:** Discuss and hear case studies on recent developments in containment, including Risk-MaPP.
- **Efficient Packaging for 2010:** Understand emerging packaging technologies and the latest regulatory requirements.
- **Lean, Green and Sustainable Manufacturing:** Learn how to be "lean yet green" under current regulatory, commercial and environmental pressures.
- **API (Bulk) Baseline® Guide – New Guide Review and Workshop:** Grasp the philosophy behind the Guide and apply its concepts in a hands-on workshop.
- **Heating, Ventilation and Air Conditioning: the Best Current Practice in the Industry:** Find out about the best current practices toward building robust HVAC systems.
- **Sterile Regulations, Practices and Case Studies:** Get the latest information on cleanroom regulations, including an update on the EU Annex 1 revision.

In addition, networking receptions will be held 26 and 28 November. For more information and registration, please go to www.ISPE.org/amsterdamconference. Early bird deadline is 12 October 2007. Exhibits and sponsorship opportunities are available by contacting Dave Hall, Director of International Sales, at dhall@ispe.org. PE

Regulatory Sessions, Latest in Industry Trends to be Presented at ISPE Annual Meeting

ISPE will offer the best in networking and educational sessions at its 2007 Annual Meeting at Caesars Palace in Las Vegas, Nevada, USA, 4-7 November.

"Delivering Today, Transforming Tomorrow" will focus on delivering the latest in what's new and current to pharmaceutical manufacturing industry professionals and will focus on fundamentals, best practices, transformation, and innovation.

The meeting allows professionals to interact with visionaries from the industry and be an active participant in shaping the future of pharmaceutical manufacturing and biotechnology.

Keynote speakers will present timely and compelling topics including cost of quality, perspectives from the auto industry, and an insider's view of a generics facility. Speakers include:

- **Charlie Portwood,** President of the TO and PS division at Wyeth, will discuss the cost of quality considering the cost of proactive investments in technology in processes in order to maintain quality and prevent negative regulatory impact;
- **Gary Convis**, Chairman of Toyota Motor Manufacturing Kentucky and Executive Vice President of Toyota Mort Engineering and Manufacturing North America, will discuss the role of management in lean manufacturing, along with its commitment to a "customer first" philosophy; and
- **Uri Boneh**, Director of Global Engineering for Teva Global Generic Resources, will speak about Teva's Jerusalem oral solid dosage plant recently completed and approved by the US Food and Drug Administration.

Sessions will include regulatory workshops that will provide ongoing interaction on Product Quality Lifecycle Implementation (PQLI), Risk MaPP,

Annual Meeting Featured Events

Communities of Practice
Several COPs will sponsor two round table events 4 November. For more information on COPs, please visit www.ISPE.org/AMroundtables.

Facility of the Year Award
In addition to the educational offerings, the overall 2007 Facility of the Year Award winner will be announced for the first time at the Annual Meeting, selected from the overall category winners which were announced at INTERPHEX*2007*. Those category award winners include Cook Pharmica of Bloomington, Indiana, USA; Genentech of Ocean City, California, USA; Shanghai Roche Pharmaceuticals, Ltd., of Shanghai, China; Taiyo Pharmaceutical Industry Co., Ltd., of Takayama City, Japan; and Vetter Pharma-Fertigung GmbH & Co. KG, of Ravensburg, Germany. Representatives from those companies will be on hand, and one will be named overall FOYA winner and be awarded a crystal trophy. For more information, visit www.facilityoftheyear.org.

ISPE Membership and Awards Ceremony
One of the most exciting parts of the Meeting is the Membership Awards ceremony, to be held 6 November. The winners of the ISPE Member of the Year, Company of the Year, Affiliate or Chapter of the Year, International Student Poster Competition winner, among many other awards will be revealed.

Certified Pharmaceutical Industry Professional (CPIP℠)
Workshops for this new certification will be held 5 - 7 November. For more information about workshop, and to learn more about CPIP testing dates and criteria, please visit www.ISPE.org/CPIP. In addition, special recognition will be given to those who have passed the Certified Pharmaceutical Industry Professional examination.

Table Top Exhibition
Held 4-6 November, the exhibition allows participants to showcase products and services from the industry. For information, contact Dave Hall at +1-813-960-2105 or dhall@ISPE.org or visit www.ISPE.org/annualmeeting/exhibits.

Networking Opportunities
From learning new and better processes, to realizing that others share the same concerns and face the same obstacles that you do, to meeting new friends, ISPE makes sure to integrate opportunities for networking at every turn. During sessions and round tables, but also during breaks, meal time, and special opportunities in the evenings, the ISPE Annual Meeting is a great place to make new and lasting friendships.

Social Opportunities
ISPE meticulously designs programs for spouses and guests that they will enjoy thoroughly while you're at meetings. There are also tours and parties for delegates that you will enjoy and remember for a long time!

...ISPE Annual Meeting

Continued.

personalized medicine, nanotechnology, real world project management, disposables, containment, and three newly-released ISPE technical documents.

New to the 2007 ISPE Annual Meeting, sessions will be organized by seven different tracks to help attendees chose the events that best meet their needs, or allow them to cross-train or gain insight in an area of interest outside their fields. These tracks and sessions include:

Regulatory/Compliance:
- Design Standards for the Pharmaceutical Industry (Round Table Discussion)
- Product Quality Lifecycle Implementation (PQLI): A Practical Approach to QBD
- PQLI Design Qualification & Design Review
- Quality by Design, Cost Savings of an Integrated Approach

Facilities and Engineering:
- Legacy Systems: Maintaining a State of Qualification
- Vivariums, Operation, Design, Construction, Costs
- Critical Utilities: Hot Topics, System Design, Materials Selection
- Latest Trends, Laboratory Design
- Sustainable Design
- Current Trends in Design, Construction, and Delivery of Biopharm Facilities

Manufacturing:
- Collocation of Development and Commercial Manufacturing
- Importance of Science and Engineering Link in Technology Transfer
- Delivering While Transforming: Advance Drug Delivery Systems
- Disposables
- Lyophilization, 21st Century
- Isolator Technology
- Nanotechnology – Future Challenges for Worker Safety
- Bioburden Concerns in Aseptic Processing
- Operational & Business Excellence Workshop: Supporting Strategic Initiatives

Innovation:
- Community of Practice (COP) Round Tables
- Pandemic Flu Preparedness
- Airborne Contamination Control (HVAC)
- What's New in GAMP®5?

Project Management:
- Latest Innovations in Project Management Tools
- Control of Project Finance
- Risk Mitigation in Ultra Fast Project Delivery
- Risk Management, A Business Perspective
- The Real World of Project Management

Investigational Products:
- Innovation and Strategic Partnerships in Investigational Products (IP): A Winning Combination
- Innovation and Strategic Partnerships in IP: A Winning Combination

Guides and Guidance Documents:
- API (Bulk) Baseline® Guide – An Applications Workshop
- Changes to C&Q Baseline Guide: Risk-Based Qualification, Case Studies
- Reliability Centered Maintenance; Implementation of Maintenance Systems to Drive Best Practices; ISPE Baseline® Guide, Volume 2, Oral Solid Dosage Forms

Please note that three of these sessions were newly added since the ISPE brochure was mailed.

Please visit www.ISPE.org/annualmeeting to find out more about sessions, networking, and other exciting activities we have planned for you.

Mark Your Calendar with these ISPE Events

November 2007

4 - 7	**2007 ISPE Annual Meeting, Caesars Palace, Las Vegas, Nevada, USA**
13	Delaware Valley Chapter, Program Meeting, Pennsylvania, USA
13	San Francisco/Bay Area Chapter, Commuter Conference: FDA Inspection Panel-Technical Discussion, Novartis, Emeryville, California, USA
13 - 14	DACH Affiliate, "Pharmawasser und -dampf" SIG
13 - 14	Nordic Affiliate, EuPAT2 Event, Copenhagen, Denmark
15	France Affiliate, Dispositifs à usage unique (Single Use Device) Seminar, France
15	Italy Affiliate, Biotechnology Manufacturing Processes, Bio Industry Park Canavese, Collereto Giacosa, Turin, Italy
15	Nordic Affiliate, Affiliate Annual Meeting: Education, Training, Science-Based Manufacturing, Operating Efficiency, ICH Q8, Q9, Q10, Copenhagen, Denmark
15	Puerto Rico Chapter, Risk Management Program, Puerto Rico, USA
15	San Diego Chapter, Dinner Meeting, La Jolla, California, USA
15	United Kingdom Affiliate, Annual Meeting and Awards Dinner, "Leveraging the Value of Experience," Deansgate Hilton, Manchester, United Kingdom
20	Boston Area Chapter, Talk Shop on Project Management, Massachusetts, USA
20	Central Canada Chapter, Toronto Breakfast Seminar, Toronto, Ontario, Canada
22	Central Canada Chapter, Montreal Breakfast Seminar, Montreal, Quebec, Canada
22 - 23	**PIC/S - ISPE Joint Workshop on Quality Risk Management, held in conjunction with PIC/S Seminar on the Manufacture of Solid Dosage Forms and Forum with ASEAN/ASIA from 20-22 November organised by HSA (Singapore), Grand Copthorne Waterfront Hotel, Singapore**
26	Ireland Affiliate, Plant Tour, Dublin, Ireland
26 - 29	**2007 ISPE Amsterdam Conference, NH Grand Hotel Krasnapolsky, Amsterdam, The Netherlands**

Dates and Topics are subject to change

ISPE and PIC/S Co-Sponsor Interactive Workshop

ISPE and the Pharmaceutical Inspection Cooperation Scheme (PIC/S) will co-host an interactive workshop opportunity for industry and regulatory leaders from up to 40 nations. "Systems Approach to Quality Risk Management" will be held 22-23 November 2007 at the Grand Copthorne Waterfront Hotel in Singapore. This is the first time that PIC/S has joined with another organization to co-host a training event and the first time that PIC/S inspectors and regulators will participate in training alongside industry personnel.

The two-day, hands-on workshop will offer attendees the chance to work side-by-side with regulators from around the world, with the goal of creating a better working relationship between regulators and industry. The workshop will examine the ICH (International Conference on Harmonization) Quality Vision, and provide updates on Q8, Q9, and Q10.

"This is the first time that PIC/S has joined with another organization to co-host a training event and the first time that PIC/S inspectors and regulators will participate in training alongside industry personnel."

Attendees will gain a deeper understanding of Quality by Design (along with each separate guidance; Q8, Q9, Q10), plus build on that knowledge through dialogues and concept sharing with PIC/S regulators.

Day One

Designed for industry professionals; regulators welcome

Session 1: Plenary

- Introduction
- ICH Quality Vision: Update on ICH Q8, Q9 and Q10
- ICH Q10: Impact and Implications of Quality Risk Management on Quality Systems

Session 2: Application of Risk Methodologies Part 1

- Moving ICH to Reality: Product Quality Lifecycle Implementation (PQLI)

Session 3: Application of Risk Methodologies Part 2

- Application of Risk Management as part of Good Automated Manufacturing Practices (GAMP®)
- The Risk Methodology in the Revised API Baseline® Guide
- AstraZeneca Risk Assessment Example Applied to a Fill-Finish Facility

Session 4: Application of Risk Methodologies Part 3

- Applying ICHQ9 Principles to Setting Health Based Limits for Cross Contamination, the *ISPE Risk-MaPP Baseline® Guide*
- Application of Risk Assessment to the Cost Reduction in Utilities

Day Two

Designed for industry professionals and regulators

Session 1: Case Studies – Plenary

- GMP Inspector: Case Study 1 – "Manufacturing of Risky Molecules in Non-dedicated Facilities"
- Industry: Case Study 2 – "Risk Management in Production Systems: Environmental Monitoring and Site Master Files"

Session 2: Workshops

GMP Inspectors + Industry

- Introduction of the Case Study

Session 3: Workshops

GMP inspectors + Industry

- Introduction of the Case Study

Session 4: Report back (Plenary)

- Report Back by Group Leaders
- Q&A on Risk Management
- Summary and Conclusions

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

"Connect and Collect"

Communities of Practice Enable True Global Collaboration

Almost three years ago, ISPE launched global Communities of Practice (COPs). Now an inherent component of ISPE, COPs are enabling Members around the world to connect and share ideas while collecting valuable and relevant information.

In support of ISPE's commitment to providing opportunities for addressing emerging industry trends and increasing efficiency through networking and on-line collaboration, ISPE has enhanced the COPs with new Community "sites" launched this past summer. Since then, ISPE Members have been joining COPs by the dozens on a daily basis – from Australia to Austria, Singapore to Sweden, the United Kingdom to Uruguay – the Communities have offered a place where members can go to connect and collect.

Based on members' feedback, the COPs are working! Members are posting discussions, giving feedback about sessions, asking questions about guidances, and other issues that can help them – and their companies.

Just looking at the COP membership tells another success story. Tucked between Kalamazoo, Michigan and Cherry Hill, New Jersey are the members from Brazil, Pakistan, Romania, Saudi Arabia, Turkey, Jordan, Mumbai, Wales, Ireland, Switzerland, Italy, England, Spain, Belgium, South Korea, China, Denmark. (And that's only from the first page of one of the Communities.)

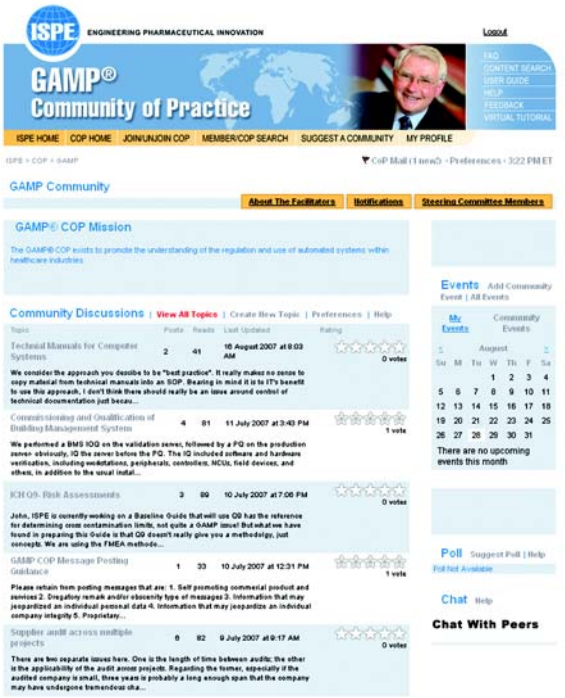
"The Communities of Practices are really taking off," according to Damian Greene, Chair of the Communities of Practice Council, and Director/Team Leader for Pfizer in New York, USA. "They are providing a niche for our Members by providing an area for them to exchange information that is critical to their workplace."

The overwhelming reason? The ease of use of the new sites.

In just days, dozens of new members were joining the Communities. As of August, more than 3,000 more people signed up to belong to a COP.

ISPE already had some excellent ways for members to communicate and network, such as E-Discussions. For instance, the Critical Utilities E-Discussions were very popular among Members. However, the beauty of the new site is that the new site brings all of these components under one roof: E-Discussions and E-Communities are now combined in one place.

"I am in awe," said Peter Vishton, Technology Engineer for Water Systems at Wyeth in Pennsylvania, USA, and a Critical Utilities COP Steering Committee member. "ISPE is really on the right track."



While the Communities are open for anyone to join, only ISPE Members have access to the best information – the ability to engage in discussions, along with participating in chats, polls, and sharing of documents.

"COPs have come a long way. The new site is compact, and everything is accessible in one spot," said Nissan Cohen, a consultant for pharmaceutical water systems based out of Louisville, Colorado, USA.

Most importantly, ISPE COPs provide instant access to others facing the same challenges as well as to the "experts" offering advice on how to resolve those challenges.

The reasons to get involved with COPs are numerous. COP members can:

- Participate, provide feedback, influence, and gain access to industry regulators, many of whom are already COP members. Participation is critical to helping technological innovation within the industry
- Learn and work together to address regional, domestic, and global issues in an open and efficient manner
- Generate and disseminate valuable technical knowledge such as technical documents, ISPE education sessions, *Pharmaceutical Engineering* articles, and E-Letters, all within the community through active participation by Community members
- Develop personal and collaborative relationships while offering the advantages of access to a wider global network
- Enhance technical excellence across multiple business units, geographical regions, and project teams

"Discussions are certainly one of the easiest and most visible modules on the site," said Scott Ludlum, ISPE's Director of Business Initiatives. "But there are many other benefits also. For one, the information is delivered directly to Members."

"The notifications are an incredible tool," said Ludlum,"Many members don't want to have to think about checking the Web site daily or weekly, and the notification e-mail reminds them

Communities of Practice...

Continued.

to do so. It makes it very convenient for users." The notification is easy for members to customize. They can set it to whatever functions they want by clicking the notification button and setting to daily, hourly, weekly, monthly, or turning it off completely.

Another great function is the ISPE Member or COP member search.

"We've enhanced the existing ISPE Member search to also include COP member search," according to Ludlum. "This function is particularly handy since ISPE Members can not only search within their companies, but can also search to find out who at their company is in their COP." One can also search by state or country.

The site is also more conducive to finding out more about other people, offering personalization to an otherwise very large Society. Other members can click on your name and read your biography. Members can add to their biographies by clicking on "my profile" and updating. Members can even post a photo – a great idea before flying off to a conference – so that it is easier to identify fellow ISPE Members at conferences and meetings.

To sign on to www.ISPE.org/COPs, just log in with your member number and password, sign up for the Community of Practice that interests you, and you can join in discussions, chats, polls, see news, events, biographies of fellow members, and more.

For additional information about ISPE COPs and to find out more, please visit www.ispe.org/cops.

Reasons to join:

- Connect with Others
- Collect Information
- Develop Knowledge
- Ability to Influence
- Easy and Convenient

Looking for Your Affiliate and Chapter News?

If you're looking for the news from your Affiliate and Chapter or Affiliate, all the news is now located in the bi-monthly *ISPEAK*, sent electronically every two months. If you haven't read their news lately, you may be missing out.

In Europe:

In the United Kingdom, find out about site visits, seminars and upcoming events; read about the Nordic Affiliate's secret to its success; In Spain, find out about upcoming October congress in Madrid and September seminars in Madrid and Barcelona; hear about Italy's Equipment Validation seminar; at the Germany/Austria/Switzerland Affiliate, read about their two-day workshop with plant tours in Southern Austria; learn about Poland's newly elected board and the fifth anniversary of the collaboration with Gdansk Medical University Student Chapter; and find out more about Turkey's Student Chapter meeting in Istanbul.

In Asia-Pacific:

Learn more about the important Australasia Conference coming in September; find out how Japan is busy with the strategic plan, incorporating the COPs (Communities of Practice) and preparing for its August meeting; how Singapore is getting ready for the PIC/S conference in November and how 400 people attended the June Singapore conference; also, find out about India's annual conference that took place in July

In the Americas:

The Affiliates and Chapters are going strong with past and upcoming events. Read more about how they are helping ISPE Members network and build their knowledge in Argentina, Brazil, Carolina-South Atlantic, Central Canada, Chesapeake Bay Area, Delaware Valley, Great Lakes, Greater Los Angeles, Midwest, New England, New Jersey, Pacific Northwest, Puerto Rico, San Diego, San Francisco/Bay Area, and South Central

To view past issues, please visit www.ISPE.org. From there you can go to the drop-down menu and look for *ISPEAK* and choose from any issue.

Make sure you read these to find out all of the great things our ISPE Affiliates and Chapters are doing!

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

ISPE Leading PQLI Industry Initiative

ISPE continues to focus on its lead industry-based initiative, Product Quality Lifecycle Implementation (PQLI). In its role as a "catalyst for change" ISPE is working with regulators in the United States, Europe, and Asia-Pacific to help industry find solutions to the challenges in implementing International Conference on Harmonisation (ICH) guidances.

The goal of these sessions is to begin to define areas where industry will be able to provide the technical framework for the implementation of Quality by Design (QbD) in regulatory submissions. PQLI examines Q8 and Q9 and identifies the subjects/terms that need to be further elaborated, and explains why there is a need for a clarification.

The PQLI sessions are an opportunity for industry leaders in science, manufacturing, quality, and engineering to continue to develop practical solutions to implementing Q8 and Q9, and ultimately Q10 (Pharmaceutical Quality Systems), and to develop a fuller understanding regarding QbD.

"It's a case study from the strategic plan of how we are a leader in innovation, how we are integrating new areas, putting science and engineering in the same room," according to Robert P. Best, President and CEO of ISPE.

The first PQLI session held in Washington, D.C., offered an exclusive opportunity for industry leaders to engage with the US Food and Drug Administration (FDA), discuss real world solutions, and help craft a pragmatic approach to implementing Q8 and Q9.

Following the Washington session, a working group continues to monitor progress, collect information, and process output into white papers, guidances, and technical documents.

Industry, regulators, and trade organization representatives met earlier this month (September) in Berlin, Germany at the first European PQLI event. This single-day event updated attendees, built on the work begun by the PQLI initiative in Washington, and continued ISPE's unique leadership in the facilitation of global solutions for the industry. Attendees also discussed future plans to present and progress PQLI, and provided critical input to help design the ISPE PQLI meetings scheduled for April 2008 in Copenhagen, Denmark.

Regulators were present to listen to audience views and to provide their perspective. In addition, attendees discussed the areas of Design Space, Control Strategies and Critical versus Non-Critical and helped develop the understanding of these issues as they relate to the Q9 Quality Risk Management Lifecycle concepts of State of Control, Knowledge Management, and Quality Management being proposed in Q10.

PQLI Timeline

Las Vegas, Nevada, USA	5-6 November 2007
Copenhagen, Denmark	9-11April 2008
Washington, DC, USA	2-5 June 2008

The PQLI initiative will continue with sessions regarding the Design Qualification and Design Review, to be held 5 - 6 November at the 2007 ISPE Annual Meeting at Caesars Palace in Las Vegas, Nevada, US. Biotechnology and Legacy Products will be addressed for the first time in the Annual Meeting PQLI sessions.

Regulators from around the world have been invited to this critical "next phase" PQLI event that is imperative to the success of the industry. Delegates will have a rare opportunity to hear the perceptions of regulators and trade organization representatives from all 3 ICH regions at Annual Meeting.

Following Annual Meeting, the next PQLI session will be held during the ISPE Conference on Innovation, 9 - 11 April 2008, in Copenhagen, Denmark. Subsequent sessions will follow as concepts are developed and input received worldwide, the conclusions from which will result in technical implementation documents produced by ISPE for industry's use in the worldwide market place.

For more information about PQLI, please visit www.ISPE.org/PQLI, or for the Annual Meeting, please visit www.ISPE.org/annualmeeting/PQLI.

A Dozen Ways You Can Get Involved With ISPE

ISPE has numerous opportunities for Members to get involved. Whether you would like to contribute as a writer, committee leader, or get involved in your own community, we encourage you to browse through some of the ways you can help strengthen your career and expand your knowledge.

From writing technical documents, to leading the latest and greatest educational sessions, to hosting discussions on our new Communities of Practice site, we are sure you will find something that piques your interest. Here are some ways you can get involved:

1 Take the Lead at a Conference

Volunteer to lead or speak at an event such as Annual Meeting, Copenhagen, or Washington Conferences. Those who have expertise in their field and are willing to share their knowledge with others make the perfect speakers at ISPE industry events.

Not only will you help others but you will also benefit from their shared knowledge when you build active discussion into your session or presentation. ISPE educational events are promoted to tens of thousands of pharmaceutical professionals worldwide. As an ISPE conference leader or speaker, you are identified as an internationally recognized expert and educator among your peers. Volunteering is your opportunity to become directly involved in helping ISPE lead the charge for innovation and excellence in our industry.

To learn more about opportunities in North America, please contact Ginger Phillips at gphillips@ISPE.org; for opportunities in Europe, please contact Olga Zvyagintserva at olga@associationhq.com; and for Asia Pacific, please contact Tarnbir Kaur at tkaur@ISPE.org. You may also visit our Web site at http://www.ISPE.org/cs/conference_leader_opps to find the 2008 schedule and speaker application to submit your proposal to speak.

2 Be an Ambassador

ISPE's Ambassador Program is designed to promote involvement and excitement about the Society through your leadership skills and enthusiasm.

ISPE Ambassadors act as representatives from your company at a variety of ISPE events, from local to international. Being an ambassador gives you the opportunity to meet others while promoting the benefits of membership and involvement at a local level – and being recognized for it. Not only does it raise your profile within the industry and your company, but you'll receive a certificate of recognition to display in your office and you will be recognized at ISPE events with a special Ambassador ribbon.

To become an Ambassador, contact your local Affiliate or Chapter President for an application, or download an application form at http://www.ISPE.org/cs/ambassador_program. Then send your completed application to your regional office:

- ISPE Headquarters: Angie Brumley, abrumley@ISPE.org
- ISPE European Office: Kristien Bossuyt, kristien@associationhq.com
- ISPE Asia-Pacific Office: Tarnbir Kaur, tkaur@ISPE.org.

3 Serve on a Committee

ISPE has dozens of committees to make sure we are anticipating and fulfilling the needs of our Members and the pharmaceutical industry. ISPE has committees for education, technical documents, the Facility of the Year Award, membership services, and much more. Here are some of the current openings for ISPE committees:

- **Student Development Committee:** Interested in participating on a committee that seeks to open doors for the next generation to enter the industry? If you enjoy mentoring, spending time with highly motivated and intelligent students who are seeking careers in our industry, or are seeking educated, talented graduates to join your team, then you might want to get involved with the Student Development Committee by contacting Tracey Ryan at tryan@ISPE.org or call +1-813-960-2105, Ext. 279.

- **Body of Knowledge Committee:** BOKC is looking for committee liaisons to join the BOKC to ensure all fields of the industry are represented. The overall mission of the BOKC is to make accessible information that fosters understanding of the sciences and technology inherent in each aspect of the development and manufacturing processes in order to promote product, process, and technological innovation. The BOKC is here to help Committees and COP members disseminate and share information, as well as aid in the integration of all ISPE products. For more information, please contact Mark Stefko, Vice President of Sales and Marketing, +1-813-739-2287, mstefko@ISPE.org, or Carol Winfield, Knowledge Management Manager, +1-813-960-2105, cwinfield@ISPE.org.

4 Write a Case Study

One of the biggest requests from Members and conference delegates has been for more real-world case studies. Here's your chance to help. Contribute to our library of industry and regulatory case studies and best practices. ISPE is developing a library of industry and regulatory case studies, or "best practices" that we hope to use in future educational programming.

If you have a real life case study that you want to share with others in your industry and add to the ISPE Education Case Study Library, you can complete and submit a form by going to http://www.ispe.org/cs/submitcasestudy.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

A Dozen Ways You Can Get Involved With ISPE

Continued.

5 Get Involved with Communities of Practices' Discussions

ISPE is known for its networking value. We're taking that a step further and enhancing your opportunity to network and collaborate on-line. At the 2005 Annual Meeting, ISPE launched the Communities of Practice (COPs). Starting with five, they have now increased to 14 COPs. These are now an inherent component of ISPE, enabling COP members around the world to connect and share ideas while collecting valuable information relevant to their jobs.

This past summer COPs started an interactive on-line community offering global networking opportunities and access to a community-specific Body of Knowledge. Now COPs have their own professional "space" on-line to communicate with other Members. You can get involved by signing up at www.ISPE.org/cops and posting to the body of knowledge by posting or answering discussion items with your relevant subject matter expertise. You'll help others by giving and sharing advice.

6 Contribute an Article to *Pharmaceutical Engineering*

Pharmaceutical Engineering is the Global Information Source for Pharmaceutical Manufacturing Professionals and is the official magazine of ISPE. The membership of ISPE, therefore your reading audience, includes people participating in multiple fields relating to pharmaceutical manufacturing. This audience encompasses engineering staff, operators, scientists, and compliance staff from biologics and pharmaceutical operating companies; vendors supplying equipment and services to these industries; regulators and government officials; academic scholars, professors, and students. ISPE provides a network for interaction and communication between all its members.

Pharmaceutical Engineering is seeking articles with a global perspective. You are invited to submit an article on one or more topics related to the themes of upcoming issues. Document your success stories on engineering applications related to the life sciences industries in your country or around the world.

For further information, see Information for Authors at http://www.ispe.org/cs/authors or contact Gloria Hall, Editor, at ghall@ISPE.org.

7 Be an Author for New *Journal of Pharmaceutical Innovation*

ISPE launched its new, scientific, peer-reviewed *Journal of Pharmaceutical Innovation* last September for the publication of research and review articles. Editors are looking for volunteers to contribute perspectives, case studies, research letters, research articles, and reviews.

The leading-edge, peer-reviewed Journal will include scientific data from a panel of distinguished authors. JPI is intended for the publication of research and review manuscripts emphasizing new and innovative methods and techniques used by pharmaceutical professionals serving all aspects of the industry including manufacturing, applied pharmaceutical science and technology in process and product understanding and control

For information or inquiries regarding editorial content, please contact Gloria Hall at ghall@ISPE.org.

8 Make Your Mark with E-Letters

E-Letters offer an alternative to writing for ISPE's magazine and journal. Sent out quarterly by e-mail, E-

One of the Best Things...

"One of the best things I ever did was to become an active Member in ISPE, according to Dave Novak, ISPE Member since 1997.

"It enhanced my career and helped me develop a better understanding of the industry and a strong network of people who I trust. Many of these individuals are key leaders and decision makers within biotechnology, pharmaceutical and government, nationally and internationally.

By taking an active role and interest in my local Chapter, I was soon voted to the local Board of Directors and eventually as an officer at the Chapter level. I am now actively involved on an international committee, which has allowed me to gain a better perspective of the ISPE organization. Through this involvement, I have gained a better understanding of the international board, committees, and leadership of this volunteer organization; its present concerns and challenges; as well as, insights into the future of the industry.

Those who make the commitment to get involved and stay active in the organization understand that ISPE provides a unique platform for the convergence of the biotechnology and pharmaceutical industries. The organization provides the resources, focus groups, leadership and commitment of its Members to research and develop new innovations and ideas occurring within academia, research institutions, industry, and government to enhance the diagnoses and treatment of disease throughout the world.

I share the same passion as other ISPE Members who are willing to commit their time to help educate and set the new standards practices and procedures for the future innovations of our industry. To put it simply... ISPE membership delivers the insight into current trends and future technologies of the pharmaceutical industry."

A Dozen Ways You Can Get Involved With ISPE

Continued.

Letters are based around our Communities of Practice and offer shorter technical articles.

You might not have enough time to write a full article for *Pharmaceutical Engineering*, or our new journal, *Journal of Pharmaceutical Innovation*, but E-Letters might allow you to make an impact and offer your technical guidance. This is your opportunity to contribute to ISPE and raise your profile.

You can write, or merely help us identify relevant and interesting sources of technical content, by directing us to the appropriate sources of information. It won't take a lot of time but it could benefit you and your professional development. To find out more, visit www.ISPE.org/e-letters or contact ISPE Technical Writer Rochelle Runas at rrunas@ISPE.org or Public Relations Manager Marsha Strickhouser at mstrickhouser@ISPE.org.

9 Contribute to Technical Documents

ISPE is seeking volunteers to serve on the Task Teams to develop upcoming Technical Documents including Baseline® Guides. These highly sought-after positions help shape the Pharmaceutical Manufacturing Industry by bridging the gap between industry best practice and FDA expectations.

The ISPE Baseline® Guides have been globally recognized as a leading source of information for new and renovated facilities. Baseline® Guide chapter writers and reviewers require a two to four year commitment, the ability and funding to participate in meetings and teleconferences, and the ability and schedule flexibility to present the Guide at ISPE seminars in North America, Europe, or Asia.

If you are interested in volunteering, please forward a letter of interest and CV to Gloria Hall, Editor/Director of Publications by e-mail: ghall@ISPE.org or fax: +1-813-264-2816. Please specify any travel restrictions you may have on the letter. If you have questions, please call Gloria at tel: +1-813-960-2105.

10 Spread the Word with 'Words to the Wise' Referral Program

With ISPE**,** there are so many ways to get involved. One of those is merely passing on the good news about ISPE and what you get from your membership. Our new "Words to the Wise" program is our Membership Referral Program, designed to reward you for discussing the benefits of ISPE with your peers. You may have been doing this for years, but now, you'll be rewarded for it. By giving ISPE your stamp of approval, you can help build your global network of industry professionals and earn benefits in the process.

Referral levels for recruitment:

- **Communication:** 1 new Member - Receive ISPE word poetry
- **Inspiration:** 3 new Members - Receive a $25 AMEX gift cheque
- **Motivation:** 6 new Members - Receive a $50 AMEX gift cheque
- **Determination:** 10 new Members - Receive a $100 AMEX gift cheque
- **Innovation:** Top Recruiter - Complimentary registration to the 2007 ISPE Annual Meeting

Send us your list and we will send each person a membership brochure with your name Member ID as the referring Member. Contact us at abrumley@ ISPE.org to request Membership brochures. E-mail your referrals to Angela Brumley at abrumley@ISPE.org. For more information and details about the program, please visit www.ISPE.com/words tothewise.

11 Sponsor an Internship for ISPE Student Members

Is your company looking for a qualified student to fill an internship position? The Student Development Committee is actively seeking internships. There is absolutely no cost to post an internship on the ISPE Web site! You and your company can decide if you want to receive responses by e-mail or directly to your company Web site.

To see the current internships and how yours might look, visit ISPE's On-line Career Center at http://www.ispe.org/cs/student_internship. If you are interested in posting a student internship, please send the position description, job requirements and any additional information to Tracey Ryan at tryan@ISPE.org.

12 Volunteer at the Local Level

There are many ways to volunteer with ISPE on the local level with your Chapter or Affiliate. For example, in California, the San Francisco Chapter, has joined with Genentech for a program that uses chocolate and enzymes to build kids' interest in science.

The new program is a collaborative effort among ISPE, Genentech, and the South San Francisco Unified School District and is one of many ISPE initiatives to educate the pharmaceutical manufacturing professionals of the future. The program can be replicated through lesson plans and brought to other elementary schools as well.

For more information on these projects, or to learn how you can bring these projects to your local schools, contact Melody Spradlin at +1-650-225-1799. Other opportunities are available by contacting your Chapter Manager or visit www.ISPE.org/cs/affiliatesandchapters.

For an On-line Volunteer Application

To download an application and find more information, please go to the ISPE Web site at www.ISPE.org/getinvolved.

ISPE Professional Certification Commission®

The ISPE Professional Certification Commission is pleased to announce award of the Certified Pharmaceutical Industry Professional (CPIP) Credential to:

Mr. Anders Brummerstedt, CPIP
Manager Computer Compliance
NNE Pharmaplan, Denmark

Mr. Damian J. Gerstner, CPIP
President
Sys-Tek, USA

Mr. Andrew A. Signore, CPIP
CEO
IPS, USA

Ms. Tiffany G. Tomlinson, CPIP
Manufacturing Manager
IDEXX Pharmaceuticals, Inc., USA

CONGRATULATIONS! FROM ALL OF US

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IPS, USA

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Novartis Pharmaceuticals Corp., USA

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IPS – Integrated Project Services, 2001 Joshua Rd., Lafayette Hill, PA 19444. (610) 828-4090. See our ad in this issue.

Parsons, 150 Federal St., Boston, MA 02110. (617)-946-9400. See our ad in this issue.

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Jim Crumpley & Associates, 1200 E. Woodhurst Dr., Bldg. B-400, Springfield, MO 65804. (417) 882-7555. See our ad in this issue.

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MKS Instruments, 5330 Sterling Dr., Boulder, CO 80301. (800) 345-1967. See our ad in this issue.

Siemens Water Technologies, 10 Technology Dr., Lowell, MA 01851. (978) 934-9349. See our ad in this issue.

Instrumentation

Hach Ultra Analytics, 5600 Lindbergh Dr., Loveland, CO 80539. (970) 663-1377. See our ad in this issue.

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Hurst Corp., Box 737, Devon, PA 19333. (610) 687-2404. See our ad in this issue.

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Active Chemical Corp., 4520 Old Lincoln Hwy., Oakford, PA 19053. (215) 676-1111. See our ad in this issue.

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Cal-Chem Corp., 2102 Merced Ave., South El Monte, CA 91733. (800) 444-6786. See our ad in this issue.

Oakley Specialized Services, Inc., 50 Hampton St., Metuchen, NJ 08840. (732) 549-8757. See our ad in this issue.

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Anhydro, 7024 Troy Hill Dr., Elkridge, MD 21075. (443) 878-4691. See our ad in this issue.

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GEA Niro Pharma Systems, 9165 Rumsey Rd., Columbia, MD 21045. See our ad in this issue.

Heinen Drying Inc., 1504 Grundy's Ln., Bristol, PA 19007. (215) 788-8196. See our ad in this issue.

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Christ Pharma & Life Science AG, Haupstrasse 192, 4147 Aesch, Switzerland. +41 617558111. See our ad in this issue.

Siemens Water Technologies, 125 Rattlesnake Hill Rd., Andover, MA 01810. (978) 470-1179. See our ad in this issue.

Veolia Water Solutions & Technologies, Marlow International, Park Way, Marlow, Buckinghamshire SL7 1YL, United Kingdom. +44 1628897200. See our ad in this issue.

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International

The **Global Harmonisation Task Force (GHTF)**[1] has issued guidance on classification of In Vitro Diagnostic Medical Devices (SG1(PD)/N045R12: Principles of In Vitro Diagnostic (IVD) Medical Devices Classification). This guidance document is one of a series that together describe a global regulatory model for medical devices. It provides guidance on the principles of classification of IVD Medical Devices.

Argentina

Anmat, the Argentinean regulatory authority,[2] has issued a regulation that sets out the requirements and documentation required for submitting applications for approval of in vivo diagnostic products. The new rules came into effect on 12 June 2007.

Australia/ New Zealand

No information of significance was added to the **Therapeutic Goods Administration (TGA)** Web site[3] in June/July 2007.

In July 2007, the Australia New Zealand Therapeutic Goods Authority (ANZTPA)[4] **released on its Web site one document for public consultation:**

- Proposed Medicine Label Statements

Under the joint regulatory scheme for therapeutic products, it is proposed that certain advisory statements will be required to be placed on medicine labels. Medsafe (New Zealand) and the Therapeutic Goods Administration – TGA (Australia) have rationalized the current statements used in their respective countries into a single set of label advisory statements. Closing date for submissions is 18 August 2007.
Australia New Zealand Therapeutic Products Authority (ANZTPA) Project Newsletter for June and July 2007 is available on their Web site[5] and contains a comprehensive list of current documents from the consultation program on the proposed regulatory framework (of ANZTPA).

Canada

Health Canada[5] proposes to amend Division 1 of the *Food and Drug Regulations* to require the submission of complete qualitative and quantitative formulation data, including a list of all Non-Medicinal Ingredients (NMIs) in a drug product, as well as the source of any human or animal derived NMIs or medicinal ingredients. This requirement will apply to all new Drug Identification Number (DIN) submissions and drug products for which a DIN has previously been issued.

Europe

In June 2007, the **European Medicines Agency (EMEA)**[6] provided via their Web site updated Post-Authorization Guidance in the form of Questions and Answers. Included are updates, in part, to Variations, Extension Applications, Renewals, and Transfers of Ownership. The Web page contains a considerable number of links to detailed information on the topics covered.

The **Committee for Medicinal Products for Human Use (CHMP)**[7] has published monthly reports from the May and June Plenary meetings held 21 to 24 May and 18 to 21 June.

The following guidelines have been prepared by the Quality Therapy Working Party:

- Guideline on Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products/ Traditional Herbal Medicinal Products in the SPC (CHMP/CVMP/ QWP/ 242720/2007).

- Guideline on Quality of Combination Herbal Medicinal Products/Traditional Herbal Medicinal Products (CHMP/CVMP/QWP/ 221930/2007).

- Question and Answer document on Applicability of Active Drug Master File (ASMF) Procedure (CHMP/ CVMP/QWP/ 249641/2007).

- Question and Answer document on implementation of PhEur Chapters 2.6.12, 2.6.13 and 5.1.4 (CHMP/ CVMP/QWP/ 255695/2007).

- Question and Answer document on Storage Conditions (CHMP/CVMP/ QWP/ 241559/2007).

The following relevant guidelines have been prepared by the Biologics Working Party:

- Draft guideline on production and quality control of monoclonal antibodies and related substances (CHMP/BWP/157653/2007).

- Concept paper on the revision of the Guideline on dossier structure and content for pandemic influenza vaccine (CHMP/166042/2007).

The following relevant guideline has been prepared by the Gene Working Party:

- Concept paper on the development of a guideline on the quality, preclinical, and clinical aspects of medicinal products containing genetically modified cells (CHMP/GTWP/ 405681/2006).

The **Committee on Herbal Medicinal Products (HMPC)**[8] has published their monthly meeting report[10] for the meeting held 8 May 2007.

The **Committee for Orphan Medicinal Products (COMP)**[9] has published their monthly meeting report[10] for the meeting held 26 to 27 June 2007.

The **Committee for Veterinary Medicinal Products (CVMP)**[10] has published their monthly reports for meetings held 12 to 14 June and 10 to 12 July. The Monthly Report of Application Procedures, Guidelines, and Related Documents for June 2007 includes a summary of the opinions issued by the CVMP in the current year and a list of adopted Guidelines and other public documents.

The **European Directorate for the Quality of Medicines and Healthcare (EDQM)**[11] has revised the document 'Content of the dossier for chemical purity and microbiological quality.' Examples of such revisions include the need to clarify the information to be given when materials are

recycled and the reference limit for triethylamine is also specified. It is also made clear that results from accelerated stability studies should be supplied when a retest period is requested to be mentioned on the CEP. Clarification is also given on the need to propose alternative analytical methods for related substances where a TLC method is described in a monograph (3.2.S.4.2).

The eighth supplement of the fifth edition of the European Pharmacopoeia (Supplement 5.8) was implemented on 1 July 2007. National pharmacopoeia documents have been updated accordingly.

The **Heads of Agencies**[12] Web site has been updated with reports from the CMD(h) meetings held 23 to 24 April, 21 to 23 May and 18 to 20 June 2007.

Sweden

The **Swedish Medical Products Agency**[13] has advised on their Web site that Marketing Authorization Holders (MAH) are required to inform the Agency whether their approved medicinal products are available on the Swedish market or not. This is in respect of the so-called 'sunset clause.' In June 2007, the Agency requested information from the MAH if their approved medicinal products were available or not as of 1 May 2006, and if any changes had occurred after this date.

Switzerland

Swissmedic[14] has provided additional information to clarify the type of changes to product information texts that can be made without pre-approval. These include minor changes to lettering, changes to packaging that do not change actual text, addition of Braille texts, and minor editorial changes. Submission of changes to pictograms is regarded as optional.

United Kingdom

The **MHRA**[15] has issued questions and answers on the so-called "sunset clause" which refers to the statutory requirements to inform the Licensing Authority of any disruptions to supply of medicines.

References

1. ICH - http://www.ich.org/
2. RAJ Pharma, Vol. 18, No. 7, July 2007.
3. TGA - http://www.tga.gov.au/media/index.htm
4. ANZTPA - http://www.anztpa.org/index.htm
5. EMEA - http://www.anztpa.org/newsletters/index.htm
6. EMEA - http://www.emea.eu.int/PressOffice/presshome.htm
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9. EMEA - http://www.emea.europa.eu/Press%20Office/comp.htm
10. EMEA - http://www.emea.europa.eu/Press%20Office/cvmp.htm
11. EDQM - http://www.pheur.org/
12. HOA - http://heads.medagencies.org/
13. SMPA - http://www.lakemedelsverket.se/Tpl/NewsArchivePage_414.aspx
14. Swissmedic - http://www.swissmedic.ch/files/pdf/04_2007.pdf
15. MHRA - http://www.mhra.gov.uk/home/

This information was provided by Peter Hagger, Pharmaceutical Research Associates (UK).