This article presents key issues in regard to pharmaceutical contract manufacturing.

Trends in Pharmaceutical Manufacturing – Key Issues When Deciding to Outsource

by Takayuki Kasai

Introduction

The pharmaceutical industry contributes a significant amount of value to worldwide healthcare and the economy.

In spite of the challenges of a global economic crisis, the pharmaceutical manufacturing industry remains an important source of strength for the worldwide economy. The industry provides thousands of stable and high-quality jobs, contributes substantially to federal, state, and local tax bases, and creates technical innovations along with economic ripple effects that strengthen other economic sectors. On the other hand, the environment of the pharmaceutical manufacturing industry has been changing drastically in the last 10 years with strong competition, due to the decrease of new drug approvals, increased development costs, and stricter regulatory requirements. In order to sustain growth, it is clear that pharmaceutical companies need to act quickly and establish restructuring plans and visions that make full use of outsourcing effectively in the four key areas: 1. Research, 2. Development, 3. Manufacturing, and 4. Sales - *Figure 1*. Having a policy and a basic strategy for outsourcing is becoming a prerequisite for surviving the strong competition from rival companies. Among the four key areas, the manufacturing sector was inherently conservative for outsourcing although it was introduced some 20 years. Today, outsourcing has become a very popular practice for most of the pharmaceutical industry. Companies are making the competitive decision to increase business through strategic manufacturing partnerships, instead of in-house manufacturing.

The Contract Manufacturing Environment: Current and Future

It is no doubt that the contract manufacturing market size is directly influenced by the pharmaceutical market. The global pharmaceutical market in 2009 is estimated to reach $750 billion, down from the $820 billion forecasted in October 2008, reflecting both the lower growth rate and currency exchange fluctuations.[1] According to the IMS forecast, the growth rate for the global

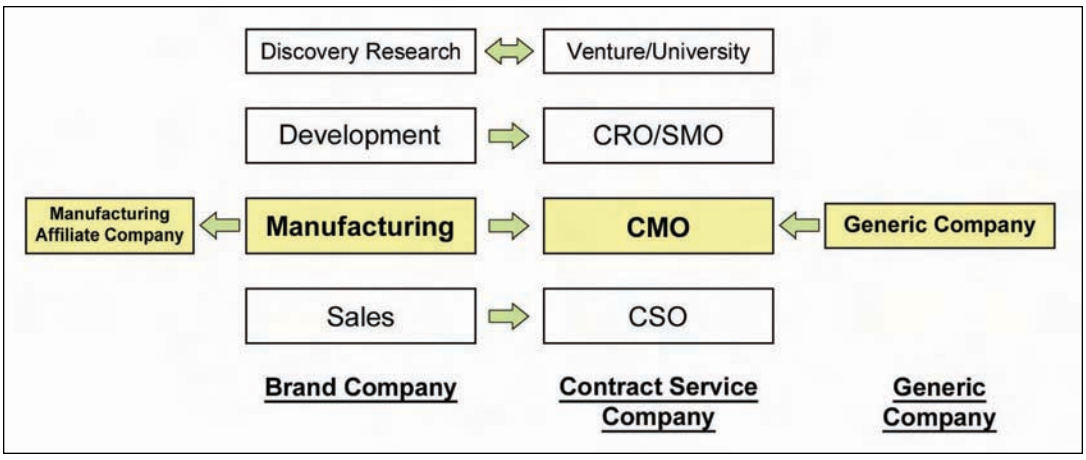


Figure 1. Four key areas for the pharmaceutical industry and the relationship to contract service companies.

Continued on page 10.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2009,
Vol. 29 No. 5

High performance teams make the difference.

Commissioning Agents, Inc.

Our teams are recognized industry leaders in developing better methods to meet your business and regulatory demands. When schedule is your problem, we are your solution.

Major services include:

- Commissioning planning, equipment start-up, troubleshooting, field execution, verification and qualification (IQ, OQ, PQ)
- Quality Risk Management (QRM) Implementation and Risk Based Qualification Programs
- Validation – Process, Cleaning, Sterilization, Computer
- Process Improvement Services: Process Analytical Technology (PAT), technology transfer, process improvement studies
- Technical services including design reviews, SOP development, and training
- Maintenance program development and implementation
- cGMP Compliance Services – audits, regulatory reviews, improvement projects, submission assistance, and comparability protocols

Achieve world class manufacturing.

Call Robert E. Chew, P.E., President
Robert.Chew@CAgents.com
+1.317.710.1530

CommissioningAgents.com

CAI

An Employee-Owned Company

"For some companies, the outsourcing of manufacturing functions has become first preference for new products where volumes are uncertain. The 10 to 12 percent growth per year of the US contract manufacturing market compared to that of the pharmaceutical market's one to two percent clearly shows this.[10]"

pharmaceutical market will continue to be three to six percent through 2013. This is assuming differing growth rates for each global region and regional differences of growth rate: one to five percent for the mature markets, which include the US – one to two percent; top five EU – three to four percent; and Japan – four to five percent, and 14 to 15 percent for China, Brazil, India, Korea, Mexico, Turkey, and Russia.[2] The following are key drivers that will contribute to the continuous growth of the pharmaceutical industry:

1. Increase in population (6.5 billion in 2005 to 7.6 billion in 2020) and rapid aging ratio over 65 years (7.3 percent in 2005 to 9.4 percent in 2020).
2. Advancement of clinical treatment and innovation in the pharmaceutical R&D sector.
3. Increasing demand for medicine or vaccines for new infectious diseases.
4. Investigation of the mechanism for various incurable diseases like Cancer or Alzheimer's.
5. Growth of the developing world market.
6. Global warming may affect healthcare in the world.[3]

On the other hand, what is the contract manufacturing market size at the moment? There are several articles that debate this question.[4,5,6,7] The articles state the size of the market to be between $17 to 38 billion in 2007; however, for the following reasons, the figures should be regarded as an estimate only. The first reason is that only a small portion of Contract Manufacturing Organizations (CMOs) are dedicated to contract manufacturing. Many contract manufacturers are fundamentally pharmaceutical companies that manufacture and sell their own products and offer contract manufacturing services in addition to their main core business. Because the majority of contract manufactures fall into this category, it is difficult to separate contract manufacturing revenue from main core business revenue within these companies. The second reason is that there are a number of pharmaceutical manufacturing processes [Active Pharmaceutical Ingredient (API) manufacturing, formulation, and packaging] that each combine further manufacturing steps. The number of processes and steps in addition to the complex in-house and outsourcing matrix make it extremely difficult for analysts to pinpoint revenues earned from contract manufacturing only.

The author's estimate for the contract manufacturing market in the fiscal year 2009 is shown below. Market share are Brand (89 percent) vs. Generic (11 percent), manufacturing costs against sales are Brand (25 percent) vs. Generic (50 percent),[8] outsourcing ratio is both Brand and Generic (24 percent).[9] The calculated result, $50 billion is relatively higher than the results shown in articles[4,5,6,7] The author concludes that the below market size is more plausible because an outsourcing ratio has been applied to compensate for potential outsourcing revenue that is not clearly reflected in financial results.

Brand: $750 billion×89%×25%×24%= $40 billion
Generic: $750 billion×11%×50%×24%= $10 billion
Total: $50 billion

In the meantime, what will happen for the pharmaceutical supply chain in the future? In the past, large pharmaceutical companies increased production capacity and relied heavily on employees to perform the manufacturing functions in-house, but this was when approval paths where predictable, there were fewer restrictions on reimbursement and high volume, and companies could reap high value for blockbuster drugs. Firms were able to extrapolate the volume of drugs into the future and invest hugely in new capacity. Today, due to much smaller development pipelines, fewer employees through corporate restructuring and mergers, the resources at large pharmaceutical companies have become exhausted and the use of third party service providers has become more cost effective. For some companies, the outsourcing of manufacturing functions has become first preference for new products where volumes are uncertain. The 10 to 12 percent growth per year of the US contract manufacturing market compared to that of the pharmaceutical market's one to two percent clearly shows this.[10] The majority of the global pharmaceutical industry is now expanding their supplier management functions to ensure that third party contractors are properly controlled and monitored in place of performing manufacturing in-house.

Service Scope of the Contract Manufacturer

At present, it takes more than 10 years to launch a prescription drug with costs averaging $1.2 billion to $1.3 billion for blockbuster type products.[11] The risks associated with bringing a drug product to market are extremely high with only 0.01% of all drug candidates actually being approved. Formulation and manufacturing issues may arise making it difficult to produce a certain compound, unforeseen side affects may force the pharmaceutical company to terminate clinical trials, or development costs may be too excessive and recuperation of development costs may be impossible within the patent protection period. In most pharmaceutical companies, manufacturing had traditionally been undervalued compared to R&D and sales and marketing functions. R&D may be thought to harbor the bright scientists who have the companies long term future in their hands, while sales and marketing's powered-up sales force bring in the money.

Continued on page 12.

Pharmaceutical Processing Systems

GEA Pharma Systems supplies the world's pharmaceutical companies with state-of-the-art solutions for the processing of active pharmaceuticals, ranging from the processing of API (Active Pharmaceutical Ingredient) to the production of solid dosage forms and sterile liquids finishing.

The GEA Pharma Systems portfolio of leading industry brands includes:

- Aeromatic– Fielder and Collette granulation/drying systems
- Buck contained materials handling systems
- Courtoy advanced tablet presses
- Niro spray drying technology
- Lyophil freeze drying systems including automatic loading and unloading

The combination of these strong brands with a deep commitment to research and development has resulted in GEA Pharma Systems establishing a leading global market position.

Engineering Excellence.

GEA Pharma Systems

9165 Rumsey Road • Columbia, MD 21045
Tel 410 997 7010 • Fax 410 997 5021
E-mail info@niroinc.com • Website www.niroinc.com

"Through this new ideology, manufacturing has begun to shift from what used to be considered a "cost center" to a "profit center." It is evident that the development of CMC within a company is not only vital to successfully advance to commercial production, but it also is a key factor for the success of pharmaceutical development..."

Manufacturing, on the other hand, has always consumed a lot of money and has often been titled a 'cost center.' However, recently a number of serious and well-publicized production problems and launch delays in conjunction with a number of FDA initiatives that focus on manufacturing and its importance have enticed many pharmaceutical companies to introduce major changes in the way they interface R&D and sales/marketing with manufacturing. Specifically, it is recognized that Chemistry and Manufacturing Controls (CMC) contributes to a more stable supply, higher quality, and cost reduction not only during the process development stages, but also throughout the entire product life cycle.

A robust production development system on many occasions can bring about breakthrough for R&D activities. One example of a breakthrough that may be achieved is an improvement in dissolution or stability for material with bad physico-chemical properties (water insolubility and solid state instability). Another, is in the chemical process development area where there also are many cases where the process chemist is assigned to establish a scaled-up manufacturing process despite the fact that the process may be considered impossible to achieve for safety, environmental, and cost efficiency reasons at the final commercial size manufacturing stage. Moreover, through the employment of CMC, increased product value during the product's lifecycle can be achieved through the introduction of orally disintegrating and sustained release formulation techniques and other additional dosage formulations resulting in the maximization of product value.

Through this new ideology, manufacturing has begun to shift from what used to be considered a "cost center" to a "profit center." It is evident that the development of CMC within a company is not only vital to successfully advance to commercial production, but it also is a key factor for the success of pharmaceutical development in areas of material supply for pre-clinical and clinical trials, process development, stability analysis, quality assurance, etc. Due to the wide scope in which CMC activities can be applied, the contract manufacturing business also has expanded to offer clinical supply and development services over and above commercial production. This is becoming a strategic area for contract manufacturers and will continue to become an essential part of their service

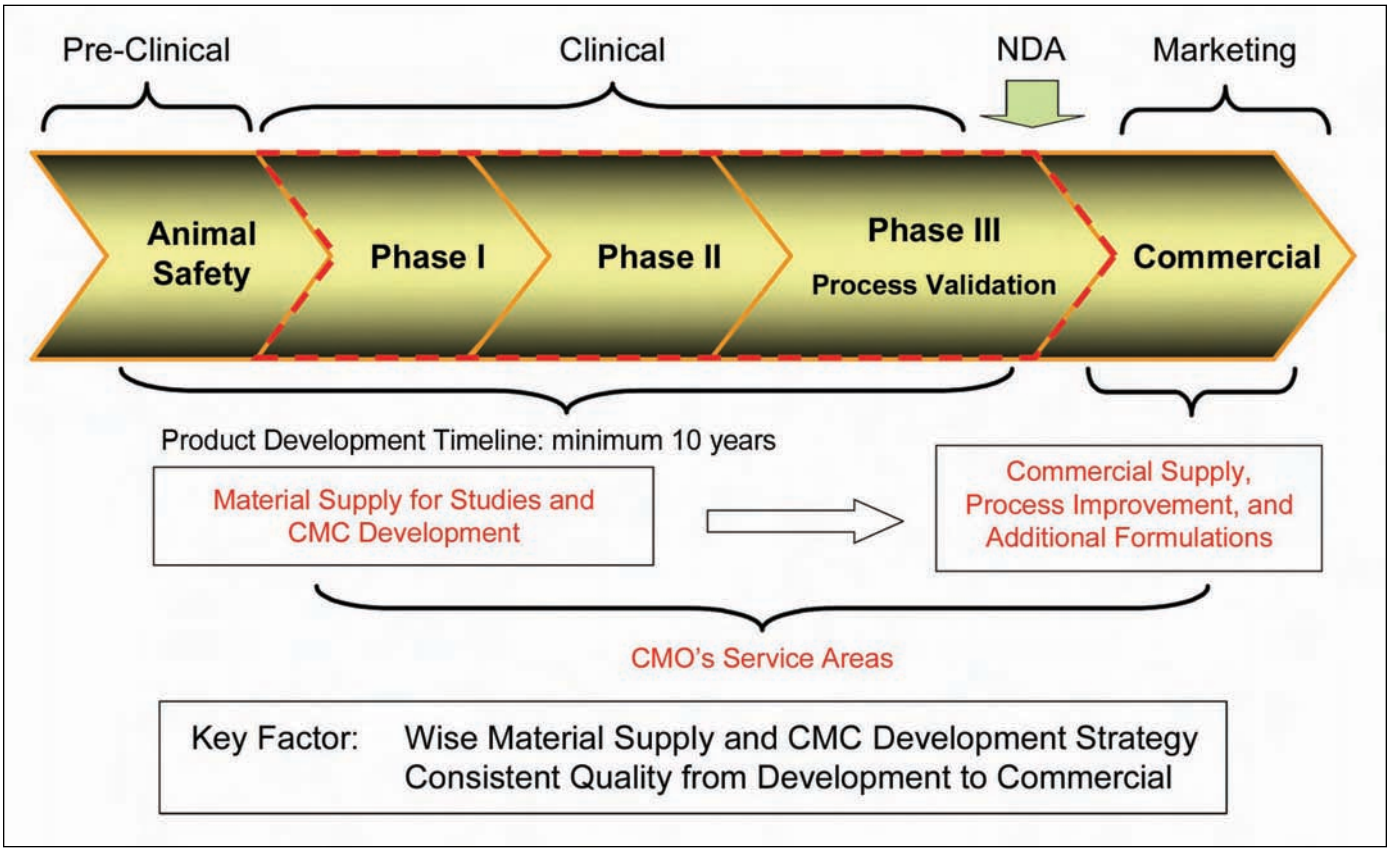


Figure 2. Product life cycle and CMO's service areas.

Continued on page 14.

With Siemens, cost-effective solutions are just the tip of the iceberg.

Siemens Water Technologies provides the largest portfolio of innovative solutions that get below the surface of all your plant's needs. Our reduction, reclaim and reuse approach helps your plant's water and energy conservation efforts, drastically reducing costs and waste production while meeting ever-increasing regulations. And with the most validated and non-validated pharmaceutical installations around the globe, experienced service teams, and fully functional factory acceptance tests (FAT), product safety and reliability are ensured, and profitability is maximized. Count on Siemens to provide more than just the tip of the iceberg. For more information, call 800.875.7873 ext. 5000 or visit **www.siemens.com/iceberg**

Answers for industry.

SIEMENS

scope in the years to come. Figure 2 illustrates the product lifecycle and service areas where contract manufacturers can currently assist pharmaceutical companies.

It is only a very recent trend for contract manufacturers to contribute to the entire value chain (API, formulation, product development and manufacturing, packaging and distribution). One of the essential factors for contract manufacturers is the ability to offer compliance with Good Manufacturing Practices (GMPs) for all manufacturing processes after the introduction step of a starting material as described in ICH-Q7, which is recognized as a common global standard. In addition, even though GMP is not required for the earlier manufacturing steps, i.e., raw materials, excipient, and packaging material, it is generally required suitable quality management (QA/QC) to ensure the quality impact to the finished product - *Figure 3*.

Outsourcing Policy and Strategy

Prior to selection of a contract manufacturer, it is in the pharmaceutical company's best interest to have first and foremost a clear outsourcing policy and strategy. Without this, benefits derived from outsourcing can easily be diminished. By establishing a clear outsourcing policy and strategy, it is important to recognize what the companies' core competences are and to possess a good understanding of current and future resources within the company (human, material, money, and in-house information) and be able to identify where outsourcing may be best utilized for existing product lines and development pipelines.

Good examples of companies that are very forward thinking when it comes to outsourcing are venture capitalist companies. These companies are largely unable to perform manufacturing functions in-house and establish comprehensive business models that focus on discovery and research activities, as well as early clinical trials up to Phase I and II [up to the Proof of Concept study (POC)] before licensing. Venture capitalists tend to concentrate their efforts on small scale API synthesis and research for other back-up and follow-up compounds in their research laboratories and rely heavily on contract manufacturers to handle process development and material supply in accordance with GMP.

Pharmaceutical companies, which are able to perform all functions (discovery, clinical development, CMC research, and commercial manufacturing) in-house, also can benefit by taking a case-by-case approach to outsourcing. Table A shows a model approach for API outsourcing. These companies must consider their current and future resources in respect to all the steps during the entire product lifecycle and determine a strategic plan for the future. The outsourcing of kg scale synthesis is not included in this table; however, there also is a growing trend to outsource this type of work.

Reasons for performing critical manufacturing steps in-house may be attributed to the following reasons: 1. consistency of quality, 2. protection of confidential information, 3. cost reduction benefit through process improvement and breakthrough, and 4. technology/know-how transfer in-house. In the case where a pharmaceutical company regards technological information to be a key factor, case 1 or 2 may be

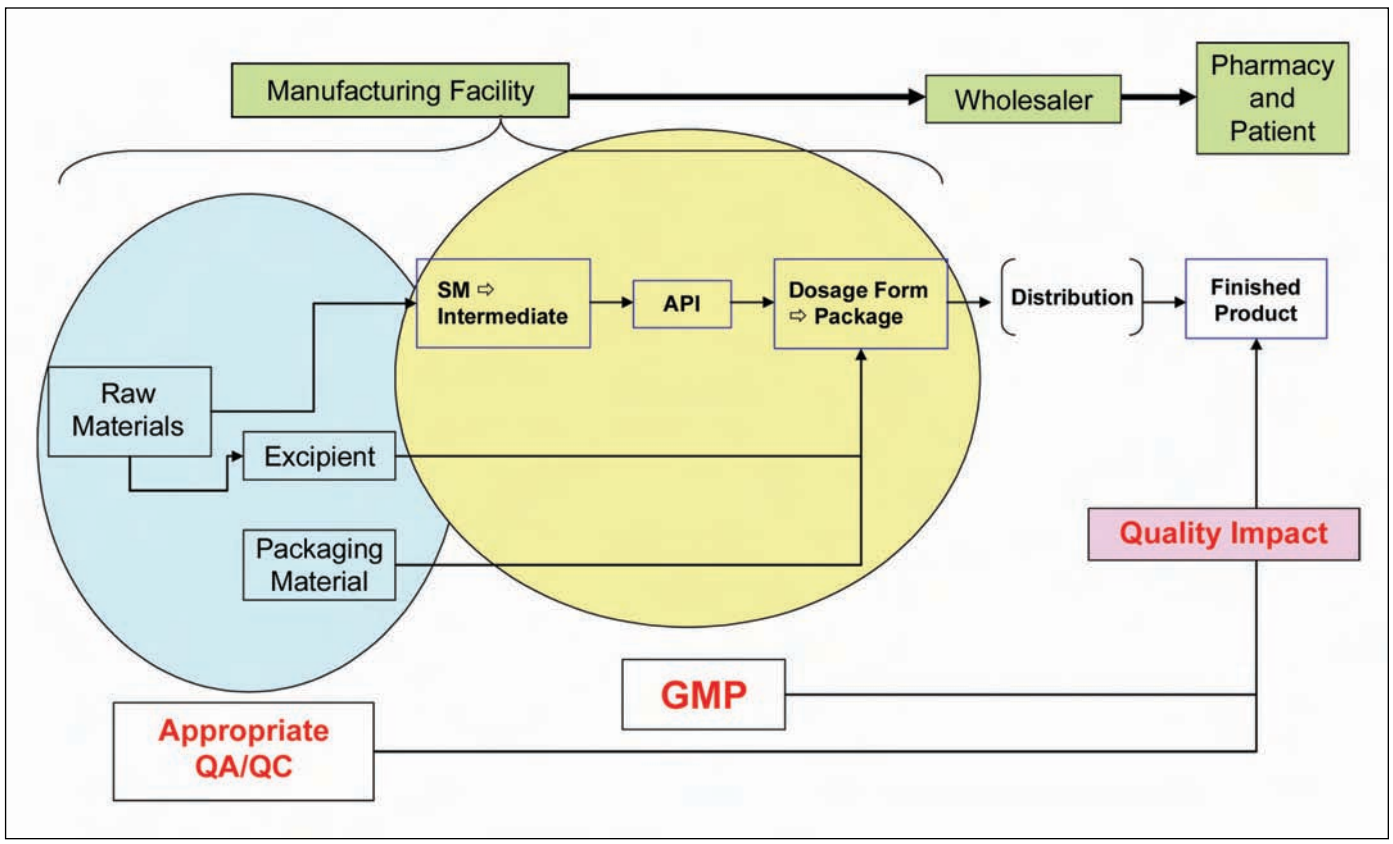


Figure 3. Supply chain of pharmaceutical products and quality requirement.

Continued on page 16.

HiProTect. Our Solution – Your Protection.

BOSCH
Invented for life

Handling highly potent products is difficult, we have the solution.

The GKF HiProTect 1700 is the industry's first true containment capsule filler for production-scale capsule filling and the first in a family of containment capsule fillers from Bosch Packaging Technology.

As drugs become more potent and regulations become more stringent, a way to separate the operator from the production area becomes increasingly important for manufacturers to consider. SMEPAC testing confirms that the HiProTect capsule fillers from Bosch offer the highest level of operator and facility safety in the industry when dealing with toxic compounds. This is achieved by incorporating a barrier system directly on the machine.

Extensive gowning is a time-consuming and expensive process, and does not ensure 100% safety. Personnel precautions can be significantly reduced when using a HiProTect machine from Bosch, thanks to the containment features built into the machine. This makes extensive PPE a thing of the past! Operators enjoy an ergonomically friendly work environment without the risk of exposure to the product.

The HiProTect maintains its integrity during both production and the automated wash down cycle. The production environment maintains a negative pressure to prevent product from escaping the system and contaminating the filling suite. A monitoring system is used to ensure proper air flow and under-pressure for containment.

Our Containment Specialists are ready to discuss your individual containment requirements and provide the customized HiProTect solution that will keep you at the leading edge of potent product handling.

Robert Bosch Packaging Technology, Inc.
Phone: +1 763 424 4700
sales@boschpackaging.com
www.boschpharma-us.com

Life Cycle	Manufacturing Step	Case 1	Case 2	Case 3	Case 4	Case 5
Pre-clinical	All Steps	In	In	In	In	In
Clinical (Ph1-Ph2)	Non-Critical Steps	In	In	Out	Out	Out
Clinical (Ph1-Ph2)	Critical Steps	In	In	In	In	Out
Clinical (Ph3)	Non-Critical Steps	In	Out	Out	Out	Out
Clinical (Ph3)	Critical Steps	In	In	In	Out	Out
Commercial (until peak sales)	Non-Critical Steps	In	Out	Out	Out	Out
Commercial (until peak sales)	Critical Steps	In	In	In	Out	Out
Commercial (peak sales to end)	Non-Critical Steps	Out	Out	Out	Out	Out
Commercial (peak sales to end)	Critical Steps	In	In	Out	Out	Out
Key: In-House: In Outsource: Out						

Table A. Case Study for API contract manufacturing during the product life cycle.

selected. If quality is regarded to be a key factor, case 3 or case 4 may be selected. It also is a possibility to select case 5; however, in doing so, it will become extremely important for a pharmaceutical company to select a reliable contract manufacturer that can ensure technological know-how, quality and confidentiality, and provide manufacturing consistency from development stages through to commercial stages.

All products have different supply volumes during the various stages of the product lifecycle. It is vital for pharmaceutical companies to perform capacity planning and production volume simulations and adjustment for development stages, as well as early, peak, and late commercial stages to determine the manufacturing site. It also is wise to determine several potential manufacturing sites. In the case of solid dosage forms, another factor needing to be considered is formulation change. Unlike a change in the API manufacturing process where changes are limited mostly to volume, it is not unusual for a formulation change to take place during development and/or commercial stages that requires an investment of new equipment, facilities, or even a new manufacturing site. For this reason, a very carefully thought-out and flexible strategy that involves a number of potential manufacturing sites including in-house manufacturing should be considered.

There also are growing instances where pharmaceutical companies do not possess the necessary technology, equipment, or facilities to perform formulation development and therefore this work is outsourced. Typical cases of this are simple formulations like suspensions and capsule filling of API for Phase I, and granule formulation design for the Japanese market for a product already sold internationally as a tablet.

In addition to the above, for solid dosage forms, it is necessary to have a good understanding of regional requirements as well. The color and size of a tablet marketed internationally may not be suitable for the Japanese market. There also may be differences in what determines a quality product versus a non quality product between different regions. Many international pharmaceutical companies struggle with the quality level applied here in Japan and the scrutiny to which product is inspected. The Japanese market has seen an average of 10 product recalls each year for the past 10 years because of biological foreign matter contamination in the way of hair, insects, and blood in the final product. In Japan, contamination of even a single hair in a lot size of 10 million tablets will be subject to a recall, unless it can be proven that the hair can be traced to only a limited portion of the lot. Foreign materials in blisters, small breakages, and wrinkles of packaging materials also are grounds for complaints.

While there may be huge financial benefits of manufacturing for the entire global market at a single site, it is extremely important to keep in mind the requirements for each of the markets being serviced. You may actually find that a lot of time and resources are being spent to maintain a cosmetic quality that is appropriate for the Japanese market and that it may actually be cheaper to manufacture or package in the Japanese market. In many instances, while manufacturing of bulk may be performed at a single international manufacturing facility, a packaging site may be employed locally due to language issues and regional preferences for packaging materials. In most cases, this is still the case with clinical trial packaging. There may be specific preferences for packaging materials and distribution used in trials between each country. For this reason, it is often important to secure several packaging sites in the countries where the trials will be conducted.

When deciding to outsource any of the formulation, manufacturing, or packaging steps during the products lifecycle, a key factor for success is to establish several contract manufacturing candidates and clearly define their strengths and weaknesses in regard to quality assurance, capacity, and speed.

Contract Manufacturer Selection

When selecting a contract manufacturer, the key areas to consider are: who and what to outsource, the extent in which to outsource (what stages of the product lifecycle), and how much volume. Data collection of potential contract manufacturer capabilities and capacities and information about in-house capabilities also are a crucial piece to the puzzle. Other areas to consider are: facility design, cost, quality (including regulatory inspection history), manufacturing technology, communication, Environment and Health and Safety (EHS)

Continued on page 18.

Innovation
makes it possible

Telstar Life Science solutions is constantly innovating to offer tailor-made solutions in high technology equipment for the pharmaceutical, biotech and related industries.

With over 45 years of experience and an international presence in more than 100 countries, Telstar is your partner to provide solutions in the following technologies:

Telstar ACE

High Containment Isolators

Telstar Celester

Sterilization Systems, WFI & Pharmaceutical Steam Generation Systems

Telstar Lyo

Freeze Drying Systems

Containment Systems
- Isolators
- Restricted Access Barrier Systems (RABS)
- Downflow booths

Sterilization Systems
- Moist heat sterilization autoclaves
- Chemical agent sterilization autoclaves
- Sterilization and depyrogenation ovens

WFI & Pharmaceutical Steam Generation Systems
- Multiple/simple effects stills
- Pure steam generators

Freeze Drying Systems
- GMP production freeze dryers
- Laboratory freeze dryers
- Loading & unloading systems
- Lyophilization support services

Laminar Air Flow Systems
- Laminar flow benches
- Biosafety cabinets
- Laminar flow booths
- Customized cabinets

Drying Systems
- Hot air drying
- Vacuum drying

Telstar®
Life Science solutions

TELSTAR LIFE SCIENCES
Josep Tapioles 120
08226 Terrassa (Spain)
T. +34 937 361 600
F. +34 937 859 342
sales.pharma@telstar.eu

TELSTAR NORTH AMERICA
1504 Grundy's Lane,
Bristol, PA 19007 (USA)
T. +1 215 826 0770
F. +1 215 826 0222
telstar.na@telstar.eu

www.telstar-lifesciences.com

Criteria	Weight	Company A		Company B		Company C	
		Rating	Score	Rating	Score	Rating	Score
Cost of Goods	9	5	45	3	27	5	45
Initial Investment	7	5	35	4	28	2	14
Quality Standard	10	5	50	4	40	3	30
Regulatory Inspection History	9	4	36	2	18	3	27
Capacity for Lifecycle	7	5	35	3	21	3	21
Technology Transfer Capability	8	4	32	3	24	3	24
Timeline for Implementation	10	4	40	3	30	3	30
Site Logistics	6	3	18	5	30	4	24
Communication	8	4	32	3	24	3	24
Confidentiality	9	4	36	4	36	4	36
EHS Management	8	5	40	4	32	3	24
Composite Score			399		310		299

Table B. Example of API manufacturing site decision.

Criteria	Weight	Company X		Company Y		Company Z	
		Rating	Score	Rating	Score	Rating	Score
Cost of Goods	8	4	32	3	24	5	40
Initial Investment	7	3	21	3	21	3	21
Quality Standard	10	3	30	4	40	5	50
Regulatory Inspection History	9	2	18	3	27	4	36
Capacity for Lifecycle	7	3	21	3	21	4	28
Technology Transfer Capability	8	3	24	5	40	4	32
Timeline for Implementation	9	3	27	4	36	5	45
Site Logistics	10	3	30	4	40	5	50
Communication	8	4	32	3	24	5	40
Confidentiality	9	4	36	4	36	4	36
EHS Management	7	3	21	4	28	4	28
Composite Score			292		337		406

Table C. Example of pharmaceutical manufacturing site decision.

management, confidentiality, capital, corporate culture, language, and people (knowledge) etc. An investigation process should be employed prior to the selection process and should be performed based on the guidelines set out in the outsourcing policy and strategy. In order to prevent the likelihood of a miss-selection, it also is a good idea to regularly update the outsourcing policy and strategy so that it is continuously in line with current management goals and objectives.

After investigations have been performed and the list of potential contract manufacturers has been narrowed down, the author strongly recommends that an on-site investigation of the contractor's facilities be made. Table B and Table C show examples of a comparison study conducted on three API and three pharmaceutical contract manufacturers. Each criteria should be assigned a value from 1~10, with 10 meaning top priority or most critical. For instance, if the timeframe, quality, and speed are regarded to be the most critical factors in the decision making process, 'Quality Standard' and 'Timeline for Implementation' should be given a '10.' Matrix type systems like the ones shown in the tables offer a very clear and objective approach to outsourcing decision making and lessen the selection risk. This type of system also can be used to evaluate in-house capacity and capability through self evaluation. In these case studies, there should be chosen Company A for API manufacturing site and Company Z for pharmaceutical manufacturing site respectively.

Contracting Process

After a decision has been made regarding which stages of the product lifecycle will be outsourced, formal contractual negotiations must take place with the selected contract manufacturer. Unlike moving forward with an in-house project, there can often be time consuming complications and/or difficulties agreeing on certain aspects of a contract. For this reason, it is very important to pay special attention to the project timeline and complete tasks as timely as possible. Figure 4 is an example of a typical project flow diagram from initial discussion through to the start of manufacturing. For early clinical manufacturing projects that do not require the purchasing of new equipment or facilities, it takes approximately three to six months from initial negotiations to production start. On the other hand, for commercial manufacturing projects that require installation of the new equipment or facility, process validation, regulatory submission, and approval, it takes approximately two to three years.

Contract Manufacturer Issues

The article thus far has primarily focused on the selection process of a contract manufacturer from an outsourcer's point of view; however, we will now look at this process from the contract manufacturer's point of view.

In the past, pharmaceutical companies have traditionally thought of contract manufacturers as 'Receivers.' In other words, a technology is transferred to the contractor and the contractor performs the tasks accordingly with very little input. Today, the outsourcing process is considerably more dynamic and contract manufacturers are often able to offer the outsourcer added value in terms of technology, quality and cost competency, and in many instances can offer value beyond methods and practices employed by the outsourcer. In reflection to this, contract manufacturers have earned the title 'Value-Creator' and a shift in the outsourcing paradigm has occurred. In realizing the benefits of contracting with a 'Value Creator,' outsourcers are aligning corporate cultures and becoming considerably more open to mutually beneficial relationships with the aim to create win-win situations.

Good business partnerships are initially formed at the start of the contracting process. It is a good practice for contract manufacturers to develop a contract agreement template so that this can be used as a basis for negotiations. If a contrac-

Continued on page 20.

Premium Design, without the Premium Price

USP Water Systems for Life Sciences

USPure Standard Water Treatment System

At Mar Cor, we focus on what we do best, providing high quality, microbiological controlled water purification systems for the pharmaceutical, beverage, cosmetic and other life science markets. Ask us to demonstrate why the USPure single skid system is the best value in high purity water.

Minncare Disinfectants

FiberFlo Filters

Water Treatment Systems

Support Services

MAR COR® PURIFICATION

A Cantel Medical Company

Competent, Consistent, Compliant

ISO 13485:2003 Certified • Mar Cor Purification • 800-633-3080 • www.mcpur.com

tor does not have a template, they are more likely to be in a weaker position during negotiation procedures and may end up adopting the outsourcer's standards despite the standards being inadequate or unfair.

Drafting contracts generally consumes a lot of time. In order to lessen the time it takes to draft and approve a contract, it is often a good idea to establish a business term sheet. The business term sheet should include, the price,

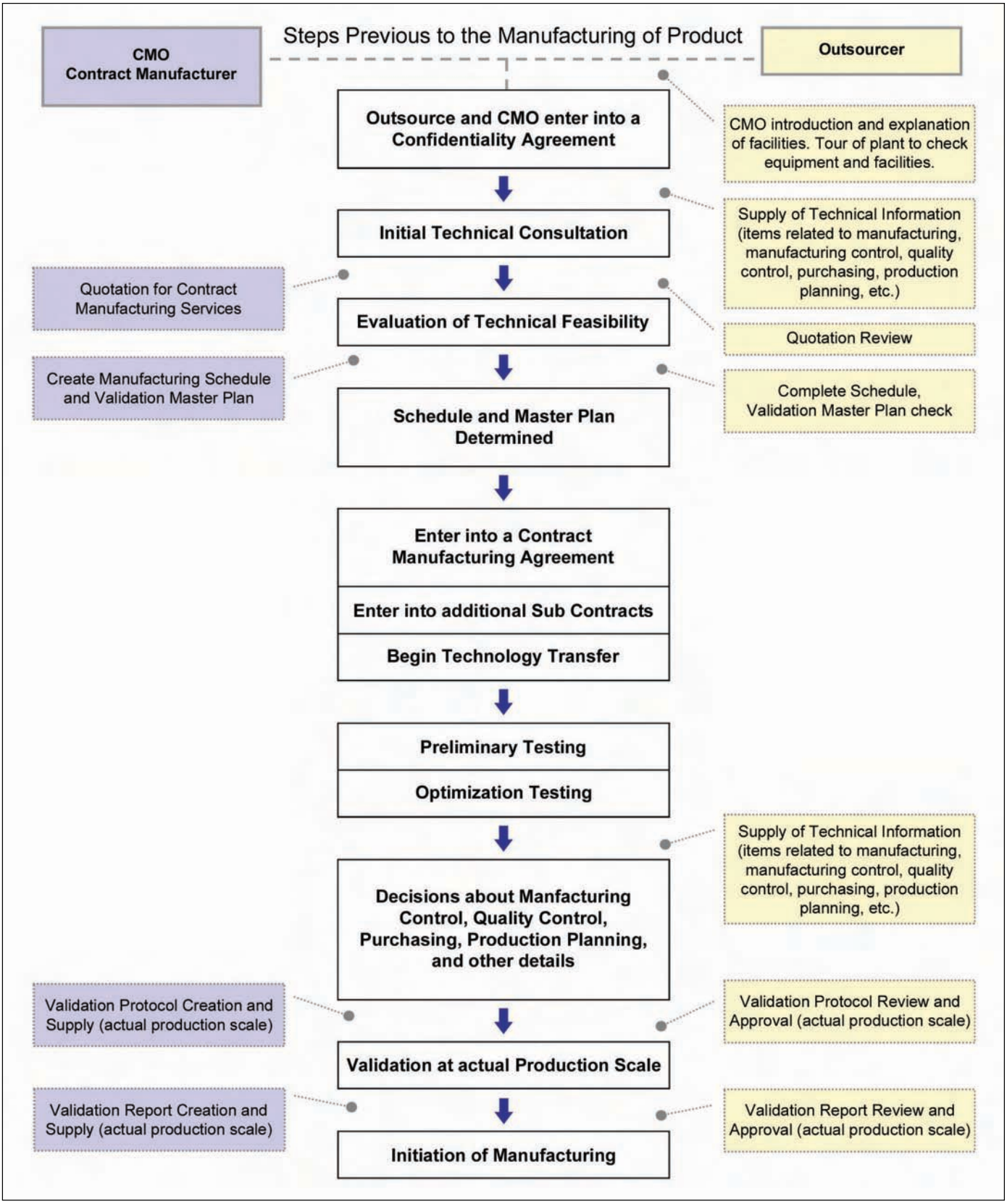


Figure 4. Typical contract manufacturing flow.

Continued on page 22.

ARE YOU RELYING ON SAFETY PRODUCTS THAT *"SHOULD"* WORK?

FIKE IS COMMITTED TO RELIABLE SAFETY SOLUTIONS THROUGH RESEARCH, NEW TECHNOLOGIES, AND EXTENSIVE TESTING.

EXPLOSION PROTECTION • PRESSURE RELIEF • TESTING SERVICES

- Comprehensive selection of ASME, CE and 3-A rupture/bursting discs
- High performance explosion vents, specifically designed for sanitary applications
- Complete line of products designed for CIP/SIP applications
- Dedicated team of combustion engineers and pressure relief experts

DON'T LEAVE THE SAFETY OF YOUR BUSINESS TO ANYTHING LESS THAN THE MOST RELIABLE, PROVEN PRODUCTS.

EXPLOSION VENTING

EXPLOSION SUPPRESSION

RUPTURE DISCS

FULL-SCALE TESTING

Fike®

WWW.FIKE.COM

PROVEN PERFORMANCE, QUALITY AND RELIABILITY FOR OVER 60 YEARS

Visit us at Interphex Canada and the Chem Show

1-866-758-6004

"The pharmaceutical industry has great opportunity for continuous growth. Within this industry, manufacturing also is expected to experience positive growth because there continues to be a need for innovation related to stable product supply, consistent quality, and cost competition."

price adjustments, required investments, manufacturing volumes, payment terms, contract length, and forecasting. Price adjustment clauses are possibly the most important. For contract manufacturers, it is extremely important to secure the absolute minimum amount of payment for services when manufacturing volumes are at their lowest due to unforeseen external environmental factors. At the same time, cost pricing for the different volume sizes in addition to the negotiation of a minimum volume also should be established. Other areas that also are important to include are clauses related to facility cost sharing, insurance fees in the case of lot failures or unforeseen disasters, and intellectual property.

It is now common practice to negotiate a quality agreement in addition to the contract manufacturing agreement. The quality agreement normally includes specific details related to the quality of the product, the term of the quality agreement, and the notification system of who to contact when certain circumstances arise. Other areas covered are GMP compliance issues, maintenance of testing methods and specifications, the right to audit the contract manufacturer's facility's, procedures to follow if notification from a regulatory authority is received and clauses related to third party contracting, change control and validation, deviation and Out of Specification (OOS) notification, annual product review, documentation storage, stability testing, reference sample storage, and complaint/recalls. While it is important for contract manufacturers to establish their own quality agreement template, many of the requests being made will be a result of the pharmaceutical company's corporate policies. Again, having your own agreement will help during the negotiation process.

Conclusion

The pharmaceutical industry has great opportunity for continuous growth. Within this industry, manufacturing also is expected to experience positive growth because there continues to be a need for innovation related to stable product supply, consistent quality, and cost competition.

The CMC function also is an extremely important role within companies because this is where new potential products are discovered and nurtured, ultimately leading to the generation of profit for the developing company and the industry as a whole. At the development stage, CMC not only covers clinical supply, but also many critical development areas that lead to the final goal of product launch.

The current philosophy of the pharmaceutical industry is that in these times of economic difficulties and hardships, it is not considered a reasonable approach for all manufacturing and development activities to be performed in-house. There are too many benefits related to cost, human resource, material management, and speed to competitively conduct all development activities in-house. A strategic approach to outsourcing is required for all stages of the product lifecycle and a clear selection guideline should be established.

For contract manufacturers, on the other hand, quality, cost competition, and the ability to offer a stable and on-time product supply will continue to be key. The adoption of additional 'value added' competencies like "Kaizen" or "Continuous Improvement" in terms of both cost and quality also will become important areas for contract manufacturers to focus on in the future.

There is absolutely no doubt that contract manufacturing will continue to become an increasingly significant part of the pharmaceutical industry during all stages of the product lifecycle. The future will see an increasing level of strategic partnerships and alliances between pharmaceutical companies and contract manufacturers with the ultimate goal of creating mutually beneficial relationships.

References

1. IMS Health News Releases, "IMS Health Lowers 2009 Global Pharmaceutical Market Forecast to 2.5-3.5 Percent Growth," 22 April 2009.
2. IMS Health News Releases, "IMS Health Forecasts 4.5-5.5 Percent Growth for Global Pharmaceutical Market in 2009, Exceeding $820 Billion," 29 October 2008.
3. PricewaterhouseCoopers Japan, Pharma 2020: Vision, pp 2-3.
4. Indian Business Journal, 14 June 2007.
5. Business Insights "Contract Manufacturing Strategy: Market Developments, Technology Transfer and Key Success Factor," May 2008. http://www.chidb.com/Business_Insight/descriptions/contact_manufacturing.asp
6. Jayakumar, P .B., "Global Pharmas Prefer Emerging Drug Makers Over Indian Giggies," 8 January 2008. http://www.rediff.com///money/2008/jan/08pharma.htm.
7. Business Insights, "Pharmaceutical Outsourcing Series, Contract Manufacturing," http://www.globalbusinessinsights.com/pharmaceutical_outsourcing/pharma_outsourcing_CMO.htm
8. Akio S., "Seisakuken News," *Office of Pharmaceutical Industry Research,* Vol. 26, 2008, pp 32.
9. Hussain M., Fenella S., "Contract Manufacturing Competition," *Contract Pharma,* March 2008.
10. Swati C., "Outsourcing in Pharmaceutical Industry," Bionity.com Articles. http://www.bionity.com/articles/e/49803/
11. PhRMA "Pharmaceutical Industry Profile 2009."

About the Author

Takayuki Kasai is the President of Bushu Pharmaceutical Ltd. in Japan. He graduated from Tokushima University and received an MS in organic synthesis for hetero-cycle compounds. He has a wealth of experience in the pharmaceutical analysis and manufacturing areas, including analytical research, physicochemical property, stability, degradation path, and establishment of specifications and test methods for new drugs, DMF/NDA preparation, chemical process development/improvement, and CMC project management. He was head of clinical manufacturing during his 20 years at Shionogi & Co., Ltd. Also during his time with Shionogi, he trained at Schering-Plough in the US for two years. He was an original member of Japanese PDA API Committee established in 2001 until his appointment of President at Bushu Pharmaceuticals. He is currently the Chairman of the Saitama Prefectural Pharmaceutical Association. He can be contacted by telephone: +81-49-233-4651 or by email: takayuki.kasai@bushu-seiyaku.co.jp.

Bushu Pharmaceuticals Ltd., 1 Takeno, Kawagoe, Saitama, 350-0801, Japan.

Change Management during Offshore Outsourcing: Success Factors for Implementation

by Dr. T.R. Ramanathan

This article discusses the nature of organizational change with respect to offshore outsourcing of IT activities in the different Information Systems Departments (ISDs) of a global pharmaceutical company and examines the effectiveness of approaches used to manage this change.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2009,
Vol. 29 No. 5

www.ISPE.org

Introduction

The business environment for large pharmaceutical companies has changed considerably in recent years. The cost of developing a new drug (Figure 1) has risen nearly four times to $1.3 billion since 1987[1] and pharmaceutical companies are now spending an average of 17 percent of sales (Figure 2) or about $3 billion per year on R&D activities. At the same time, pharmaceutical companies also are witnessing an industry-wide decline in R&D productivity - *Figure 3*. These pressures are prompting an increasing number of pharmaceutical companies to undertake various change initiatives ranging from mergers and acquisitions and partnering with biotechnology firms to strategically outsourcing a number of activities across the value chain, including support functions such as Information Technology (IT), human resources, and finance to control costs and improve revenues by reducing the time-to-market of new drugs.

As pharmaceutical companies seek ways to boost the efficiency of their processes and streamline complex internal operations, their interest in using offshore outsourcing to meet these objectives has grown significantly in recent years. For example, AstraZeneca signed a multi-million dollar, five-year outsourcing agreement with the Indian IT firm Infosys in December 2008, which provides end-to-end IT application maintenance services to the company's global operations in areas such as manufacturing, supply chain, finance, human resources, and other corporate functions. Similarly, Bristol-Myers Squibb announced in September 2008 that it had signed a new 10 year, $550 million contract with Accenture for providing a range of finance and accounting and IT application development and maintenance services, thereby extending the scope and duration of an existing four year outsourcing agreement. Although the industry's interest in offshore outsourcing originally stems from lower labor costs for IT services, many pharmaceutical companies are now rapidly moving to capture gains beyond labor cost savings in back-office operations.[2] With the recognition of offshore outsourcing as a key business strategy by more and more companies, there is less emphasis on cost reduction and more emphasis on flexibility and speed required to meet changing business needs, access to new technologies and expertise, productivity gains, quality improvements, and revenue growth.

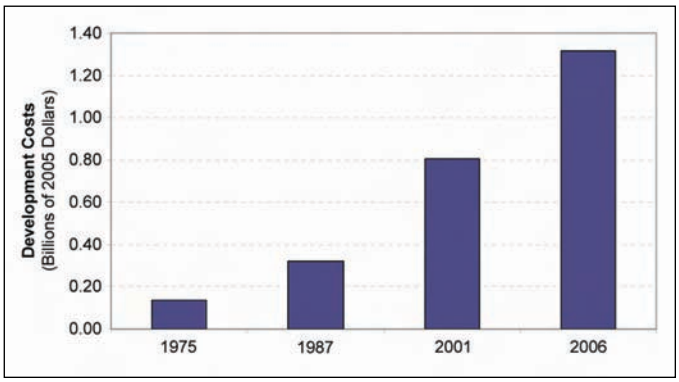
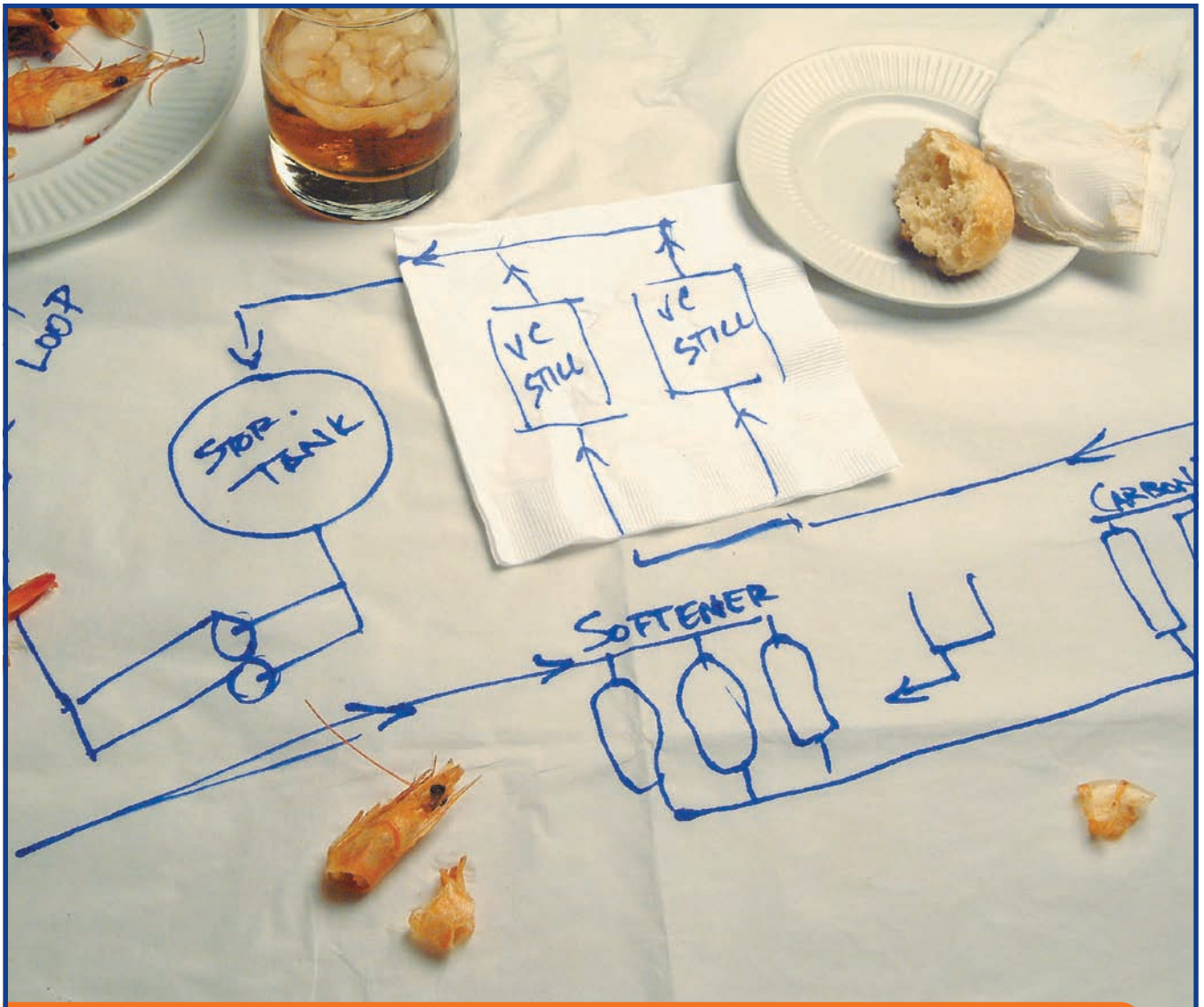


Figure 1. Growth in drug development costs – 1975 to 2006. (Source: Pharmaceutical Research and Manufacturers of America (2008))

While some experts have suggested that the overall demand for offshore outsourcing has reduced in the wake of the current global economic slowdown, the impact of the economic downturn on offshore outsourcing appears to be of lesser significance in the pharmaceutical industry than in other industries. The reason is because, even prior to the onset of the economic downturn,

Continued on page 26.



VAPOR COMPRESSION IS JUST THE BEGINNING OF WHAT WE DO.

Innovative Solutions For Purified And WFI-Grade Water And Pure Steam.

It was a big idea that simply got bigger. Today, MECO has grown to provide expert guidance and customized solutions for every phase of water and Pure Steam generation. Whether you need a particular product, a specialized service or an entire water plant designed and built from scratch, MECO delivers. To see for yourself, visit mecobiopharm.com or call 1-800-421-1798.

MECO

MECO NO BOUNDARIES PROMISE

PEOPLE | PRODUCTS | SERVICE

US _ UK _ Singapore _ UAE _ 800-421-1798 _ mecobiopharm.com

12505 Reed Road, Suite 100, Sugar Land, TX 77478

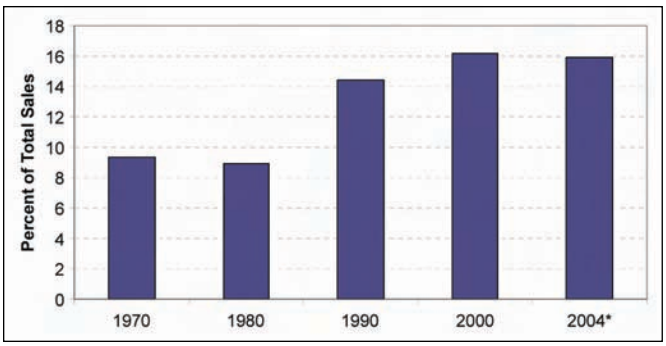


Figure 2. Pharmaceutical industry R&D expenditures as a percentage of total sales – 1970 to 2004. (Source: Pharmaceutical Research and Manufacturers of America (2005))

pharmaceutical companies had recognized the need to reduce their ratio of Selling, General and Administrative (SG&A) expenses to net sales, and had already begun to outsource support functions and indirect procurement in order to reduce their overhead costs. In addition to having relatively strong interests in reducing the cost of support functions, their focus for cost reduction lies in removing cost from major industry-specific processes, such as warehousing and logistics, customer account administration, adverse events processing, litigation case processing, and patent related issues.[3]

With pharmaceutical companies turning to offshore outsourcing to achieve cost efficiencies and shorten product lifecycles, many offshore initiatives are failing to meet performance expectations because offshoring causes far-reaching changes throughout the organization, which are often poorly managed. Despite the proliferation of models and best practices to aid the successful diagnosis and implementation of change efforts, two out of every three change initiatives fail, according to a recent global survey of 3,199 executives by McKinsey & Company.[4, 5] The survey revealed that managers immerse themselves in an "alphabet soup of initiatives" without fully understanding the nature and process of corporate change. As a result, there is a growing need for organizations to understand how change related to offshore outsourcing occurs so that they can manage this change process more effectively.

Against that background, the author's research study aimed to understand: 1) the nature of organizational change with respect to offshore outsourcing of IT activities in the different Information Systems Departments (ISD) of PharmaCom (pseudonym) and 2) to examine the effectiveness of approaches used to manage this change so that lessons may be drawn from these experiences. The research employed a qualitative case study approach to gain an in-depth understanding of the processes, organizational factors, and effects of change related to offshore outsourcing in three ISDs of the company (i.e., R&D, Sales and Marketing, and Corporate Information Systems Group). These ISDs served as the units of analysis for the investigation, and an analysis of similarities and differences of the offshore program outcomes across these ISDs provided the basis for drawing conclusions. The author hopes that policy makers and change managers will be able to use the results of the study as well as the recommendations to enhance the planning and implementation of future offshore outsourcing initiatives in order to achieve positive organizational outcomes.

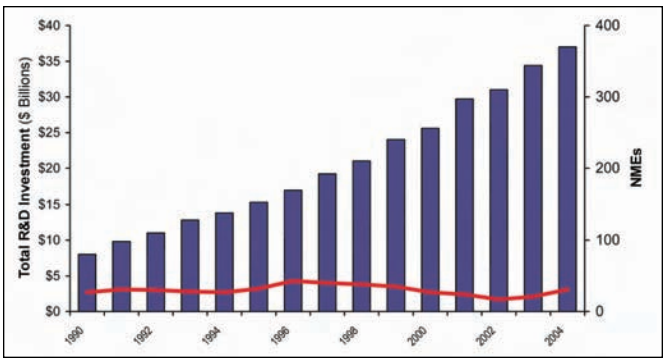


Figure 3. Pharmaceutical industry productivity vs. R&D investment. (Source: Pharmaceutical Research and Manufacturers of America (2000, 2008))

Case Study

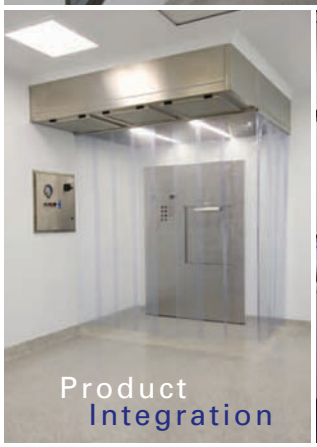
PharmaCom, a global pharmaceutical company with access to worldwide resources and markets, is not insulated from any of the forces impacting the pharmaceutical industry that were previously described. In order to address these challenges, PharmaCom undertook a detailed review of its strategy and concluded that its current structures and processes, developed over many years, were too complex and no longer conducive to sustaining strong business performance. It also was concluded that PharamCom needed to respond to the changes in the business environment being observed in many of its markets, in particular increased governmental restrictions imposed on healthcare spending and impending patent challenges to two of the company's top-selling drugs.

In 2003, PharmaCom's top executives decided to launch a set of company-wide reshaping initiatives aimed at improving the quality of its processes and business, focusing on value-adding activities, eliminating inefficiencies, and freeing resources so that the company could invest more in future growth. These change initiatives were intended, in the long term, to improve resource allocation and to increase the quality of PharmaCom's business by creating the level of excellence needed to implement its business strategies, while continuing to generate sustainable growth in a more challenging environment. The management projected that, in just less than three years, $625 million a year could be reallocated on a permanent basis as a result of these initiatives. The projected financial savings were seen as validation that the new initiatives ensured the company's future in terms of new products, while protecting its earnings growth.

Executive management took a business function-based approach to implementing the reshaping initiatives. A range of individual initiatives were proposed in several geographical regions and in the Sales and Marketing, Research and Development, Manufacturing, and Finance and Administration Business Functions. As an example, in Finance and Administration, the management initiated several projects to improve quality and overall productivity and efficiency, including one

Continued on page 28.

A Single Resource...



for TOTAL Cleanroom Confidence.

Planning & executing the right cleanroom solution for your critical process.

AES is your single resource to deliver fast track solutions for Pharma & BIO applications, such as:

- **API Clean Containment**
- **Fill/Finish Processes**
- **Blow/Fill/Seal Facilities**
- **EU/Grade A Laminar Flow Upgrades**
- **Low cost ISO 8/CNC Macro Environments**
- **Cell Manufacturing Facilities**

With the AES Pharma Wall System, combined with our expert knowledge of HVAC and process integration, let us show you how the AES "single resource" team can deliver maximum value to your cleanroom investment.

Call Grant Merrill at 888-237-2532 (ext. 139) to arrange your free consultation today.

aes
Clean Technology, Inc.

1-888-AES-CLEAN ext. 139
237-2532

aesclean.com

focused on implementing an offshore outsourcing strategy for IT projects and services. The Sales and Marketing ISD had already experienced success with offshore outsourcing on IT projects (on a smaller scale) suggesting that this approach was worth exploration on a larger scale at the enterprise level.

The management proceeded with caution, redirecting only a portion of the total external IT spending to offshore companies. The rationale was that the company could first test the long-term feasibility of the offshore IT outsourcing strategy, while being sensitive to and mitigating initial fears and concerns of employees by demonstrating management's ability to manage offshore outsourcing without negatively impacting internal staff. The offshore IT outsourcing initiative was led by a Change Management Team (CMT) comprising of senior staff members from the different ISDs. The CMT was charged with planning and implementing the offshore initiative within the different ISDs, taking into account its potential impact on the company's business and on the ISDs' human resources. With the CMT in place, the executive leadership had created the organizational structure and conditions necessary for the adoption of offshore IT outsourcing in the company.

During the latter part of 2003, the CMT organized workshops to examine lessons learned from the previous offshore IT outsourcing experience. The CMT members also received a full day of education from both internal experts and external agencies (such as Gartner and Infosys) in order to help them overcome their initial fear of offshore outsourcing. More specifically, the workshops examined offshore trends in application software outsourcing, potential benefits and drawbacks of the different offshore delivery models (i.e., onsite, onshore, nearshore and offshore – see Table A for a list of pros and cons of these approaches), myths and realities regarding cost savings, factors to consider in supplier selection, and critical success factors. These workshops also reviewed several case studies from various industry sectors in application software outsourcing, focusing on business challenges that were driving outsourcing decisions, the scope

Delivery Mode	Benefits	Risks	Outsourcing Strategy
IN-HOUSE DEVELOPMENT			
	• Security • Business Continuity • Intellectual Property Protection • Infrastructure	• High Labor Costs • Availability of Relevant Skills • Low Efficiency • Management Burden	
CAPTIVE CENTERS			
Offshore/Nearshore	• Security • Business Continuity • Intellectual Property Protection • Infrastructure • Low Labor Costs • Availability of Relevant Skills • Service Quality • Size and Quality of Labor Pool	• High Management Effort • Financial Risk (i.e. initial investment) • Start-up Costs: - Infrastructure - Hardware - Software	
GLOBAL DELIVERY MODEL			
Onsite	• Proximity to Client • Security • Business Continuity • Intellectual Property Protection • Infrastructure • Cultural Fit	• High Labor Costs • Availability of Relevant Skills	Typically staff augmentation
Onshore	• Proximity Limited to On-demand Presence at Client Site • Business Continuity • Infrastructure • Project Management Capabilities • Business Process Expertise • Fixed Cost • Cultural Fit	• Security • Intellectual Property Protection • High Costs • Hidden Costs (Travel, Communication) • Scope Changes can Escalate Costs	Project-based consulting and system integration
Nearshore	• Same Time Zone • Relatively Lower Costs • Infrastructure • Language Skills • Shared Business Culture	• Security • Intellectual Property Protection • Business Continuity • Hidden Costs (Travel, Communication) • Scope Changes can Escalate Costs	Project-based consulting and system integration, and Service outsourcing (infrastructure or business processes)
Offshore	• Low Cost • Availability of Relevant Skill Sets • Process and Methodology (Certifications) Maturity • Service Quality • Size and Quality of Labor Pool	• No Proximity to Client • Time Zone Difference • Communication/Language Issues • Security • Intellectual Property Protection • Scope Changes can Escalate Costs	Staff augmentation, project-based consulting and system integration, and Service outsourcing (infrastructure or business processes)

Table A. Pros and Cons of the major IT sourcing approaches.

Continued on page 30.

Filling x Freeze Drying x Loading / Unloading

=Experience^3

Next generation of **aseptic vial processing**

4-lane **time-pressure** dosing system **100% IPC**

Freeze dried or conventional processing of the most **diversified substances**

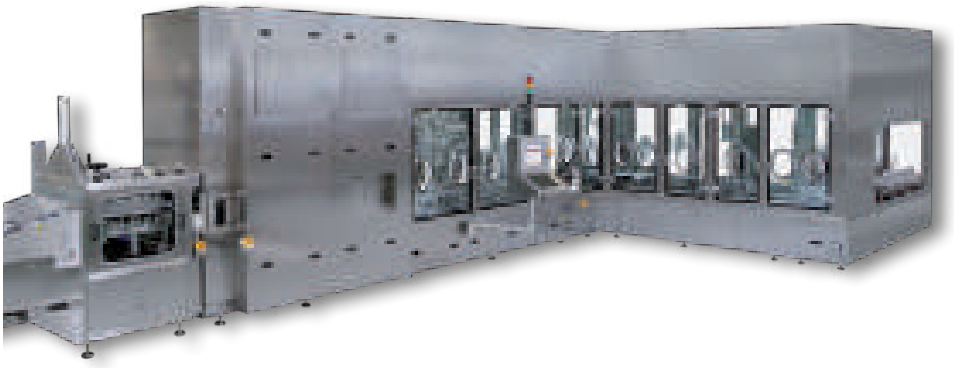
Automatic loading and unloading **freeze-drying**

Isolator design for **maximum protection**

OPTIMA GROUP

pharma

INOVA
KUGLER
KLEE



get more information on www.vial-filling.com

OPTIMA GROUP pharma GmbH, 74523 Schwäbisch Hall, Germany, Facility 35075 Gladenbach, Germany
OPTIMA Machinery Corporation, 1330 Contract Drive, Green Bay, USA

Member of

PACKAGING VALLEY Germany

of services covered by application outsourcing engagements, key factors and attributes involved in vendor selection, and criteria for measuring success.

As part of data gathering and analysis, the CMT evaluated the following risks associated with IT offshoring and identified strategies for mitigating them: threats to intellectual property; loss of control over the outsourced activity; customer dissatisfaction; impact of poor service quality; and loss of data security, business continuity, and IT skills and expertise. The CMT decided not to offshore any core IT activities, including the development or maintenance of any regulated IT systems (such as submissions, clinical trials, labelling, drug safety, etc), as outsourcing these could expose the company to unexpected risks. In early 2004, the CMT required each ISD to offshore at least one IT project or service, following the CMT's guidelines and criteria for offshoring. As a result, a total of 24 projects/services were identified from the different ISDs for offshore implementation during the first year of operation. For example, in the Sales and Marketing ISD alone, 15 projects were identified for potential offshore implementation with a number of them to be delivered on a fixed-price basis, thus representing significant savings for the ISD. To illustrate, this ISD expected to save at least $1.25 million per year from just two of these 15 projects. Similarly, the R&D ISD sought to establish an Offshore Development Center (ODC) in India, providing expertise in four critical software technologies (i.e., Documentum, Plumtree Portal, Tibco, and Informatica). The ODC, with 13 full-time personnel, was to provide software development and maintenance services in these technology areas, and represented a total annual savings of more than $500,000 for the R&D ISD.

With regard to vendor selection and sourcing, the CMT initially examined 16 vendors and selected six for more intensive screening. This process included field visits to vendor facilities in India to meet their staff and to understand their processes and capabilities. The assessment (see Table B for vendor evaluation criteria) focused on the ability of the vendors to adapt or tailor their work processes to meet PharmaCom's needs. The CMT finally selected three vendors, to which the ISDs could outsource their projects or services. A two-year outsourcing agreement was negotiated and executed with each of these vendors, providing default contractual obligations between PharmaCom and the vendors. The outsourcing agreement required each work assignment to execute a Statement of Work (SOW) with an associated Service Level Agreement (SLA) and cost schedule. The ISDs were required to follow a Request for Proposal (RFP) process for each project or service execution to competitively select a vendor from among the approved vendors.

Evaluation Area	Criteria
Company:	Vision and direction Company stability (finance, customer base) Size Location: onshore/nearshore/offshore Security Organizational culture
Technology:	Project management Software development process Quality process
Human Resources:	Skill sets People quality Retention rate Training and development

Table B. Vendor evaluation criteria.

The ISDs had considerable freedom to design and implement the necessary governance structures and organization to manage these offshored projects/services within the overall offshoring framework put in place by the CMT - *Figure 4*. The ISDs created their own Project Management Offices (PMOs) to oversee operations, handle vendor management, enforce compliance with quality requirements, and track and report performance.

Key Findings

The findings from the study suggest that a confluence of external and internal contextual pressures for change created an environment receptive to the adoption and use of offshore outsourcing at PharmaCom. The external context, particularly the economic forces, was found to be primary catalyst promoting change initiatives, such as offshore outsourcing in cost-oriented organizations. However, recent research indicates that the strength of cost pressures can vary by the sector and can depend on the competitive intensity of the sector.[6] Based on the data, it appears that the R&D productivity crisis is a necessary condition for companies in the pharmaceutical industry to adopt strategies, such as offshore outsourcing, to reduce drug development costs and to improve R&D productivity. Regulatory concerns remain an important challenge to the adoption of offshore outsourcing, reinforcing the findings of previous research by Farrel, Laboissiere, and Rosenfeld (2006). New technologies have become a significant source of competitive advantage in the pharmaceutical industry by accelerating drug discovery and development, supporting the notion that businesses have come to increasingly rely on IT to achieve and maintain sustainable competitive advantage.[7] Investment in information technologies, in particular, increase business efficiencies, while offshore outsourcing of IT services is instrumental in deriving maximum value from these investments.

Within the context of a changing external environment, the internal context further explains the rationale for the adoption of offshore outsourcing at PharmaCom. The role of the executive leadership was central to this adoption. Examination of the organization's internal (and external) environment by the top leadership appears to have led to the introduction of strategies aimed at gaining competitive advantage. Resource consideration, notably the lack of human and financial resources, was a dominant factor influencing the adoption and use of offshore outsourcing within PharmaCom. The shortage of internal IT staff to satisfy the growing demand for IT services, coupled with budget constraints, provide an important incentive to support the adoption of offshore outsourcing. Lack of internal resources was identified as a dominant factor in all three cases, validating the suggestion by previous

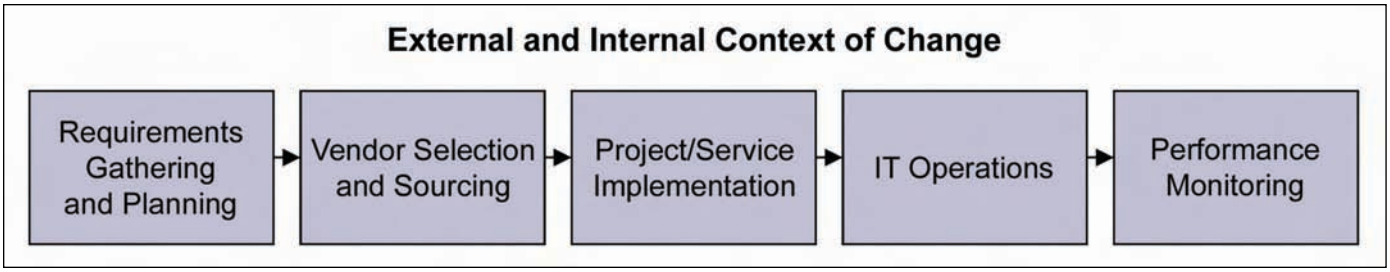


Figure 4. High level offshore outsourcing process.

research that it is the "scarcity of local talent that prompted companies in the US and Germany to hire offshore at the end of the last decade."[6] A proper understanding of the organization's internal environment (e.g., resource constraints) is necessary for leaders so that they can take into consideration these internal variables while planning a change initiative. This aspect is noteworthy in this study since in much of the change literature the focus is on external factors.

The findings also suggest that several organizational factors in combination are necessary for the successful diagnosis and planning of change with respect to offshore outsourcing in IT organizations. For example, the study found that factors, including data gathering and analysis, a solid change management team, adequate resource allocation, feedback mechanisms, and performance measurement contributed to the successful management of change. On the other hand, factors such as the lack of a sense of urgency, the lack of a vision, the failure to clearly identify the benefits of the change, lack of education and training in cross-cultural communication, and poorly designed vendor selection process were found to hinder successful change management.

With the implementation of change, the study found that various organizational factors, including management of transition to the new state, pilot projects to facilitate the assimilation of change, and proper management of day-to-day operations contribute to successful offshore outsourcing implementation. At the same time, failure to effectively communicate the vision, the directive (top-down) implementation approach, the lack of strategies to manage employee resistance, and the lack of plans to develop a fit between the change and the organizational culture were perceived as significant barriers to offshore outsourcing implementation.

Continued on page 32.

In terms of the effects of change, the study found that the main effects of the offshore initiative include performance of multiple roles by employees in change implementation and management expectations of these roles, as well as benefits of collective learning that help to take corrective actions to achieve the desired future state. Also, rewards are particularly viewed as critical for adopting new behaviors related to the change. Demonstration of positive results during the course of the change process and ensuring leadership support is linked with helping to institutionalize the change.

In sum, the successful introduction of offshore outsourcing within an IT organization and the smooth transition to the desired future state depends on the change strategy adequately addressing all of the abovementioned organizational factors. Taking these factors into account during the planning phase helps to minimize employee resistance to change and contributes to successful outcomes. In addition, senior management must make every effort to maintain high employee morale during offshore outsourcing, including treating employees appropriately by providing adequate support and reasonable remuneration deals.[8]

Implications for Change Management Practice

The issues raised in this study have implications for both policy makers as well as change managers. Many of the recommendations set out below have already been well attested by the change management experiences of organizations in other industries.

Recommendations for Policy Makers

Building Commitment to Change

Building commitment starts with communication from the executive leadership explaining the need for change. The communication must aim to sensitize employees and other stakeholders to the contextual factors, both internal and external, that have led to the consideration of the change. The employees and other stakeholders must understand why the organization is embracing offshore outsourcing and how this change will affect them. When they understand that offshore outsourcing is driven by legitimate business drivers, they are more likely to accept it. Without a clear understanding of these business drivers, they may come to view the change as unjustified and burdensome, thus increasing the likelihood of resistance to offshore outsourcing initiatives.

Aligning Outsourcing Objectives with the Corporate Vision

Successful offshore outsourcing depends on having a clear corporate vision that aligns offshore outsourcing with business objectives and a demonstration of conviction by executives that offshore outsourcing will help in realizing the corporate vision. Aligning the outsourcing strategy with business objectives can provide several potential benefits to a business, including more competitively priced products and services, greater return-on-investment, increased profit margins, growth, etc. However, aligning outsourcing objectives with the corporate vision does not itself guarantee that workers will embrace offshore outsourcing, especially if jobs will be displaced due to offshoring. Employees are less likely to resist the change when they see offshore outsourcing as improving the long-term viability of the company through increased profits and business growth. On the other hand, if they determine that offshore outsourcing is being pursued only to meet short-term cost reduction goals, including layoffs, they may resist the change.

Change Management Team

It is imperative for top-level executives to recognize that having an effective change management team (or change agents) is a critical success factor in implementing offshore outsourcing programs. This team must be powerful in terms of titles, information, expertise, reputations, and relationships[9] to be able to remove obstacles to the change and deliver on the change outcomes. More importantly, the individual team members must possess credibility as leaders and be free of self-interest and hidden agendas so that they can win the trust of the employees and other stakeholders. Also, the change management team's membership must be representative of the different departments and units impacted by offshore outsourcing, and individual team members will require change management competence to deliver the results for which they are accountable.

Executive Sponsorship

Top executives can play a crucial role in successful change management by actively participating throughout the change management process. Through the sponsorship of specific projects or initiatives, these executives can not only demonstrate their commitment to the change, but also can show that the proposed change aligns with the business objectives. Getting the projects or initiatives incorporated into the sponsors' objectives gives them the incentive to make change work.[10]

Recommendations for Change Managers

Vision for Change

Offshore outsourcing, as with any major change, requires the development of a clear vision that describes a "big picture" of the desired future state. The commitment of the change managers (assuming that the change managers are responsible for initiating the change) must flow from the clarity of the vision and it must percolate down the organization creating buy-in at all levels. A good vision is imaginable, desirable, feasible, focused, flexible, and communicable.[9] Finally, the change managers must translate the change vision to the external service providers in terms of change implementation strategy and performance goals and measures, which must be clearly understood and agreed upon by the service providers.

Communicating the Vision for Change

The importance of communicating a vision during a significant change effort, such as offshore outsourcing, cannot be overstated. Change management experts state that a vision-driven change requires extensive and creative use of communication

strategies.[11] In communicating the vision, the change managers not only establish credibility with employees, but also help to minimize employee resistance to the change.

Sense of Urgency

Change mangers can set the stage for offshore outsourcing by instilling a sense of urgency within the organization. A "burning platform" is essential to alert and motivate the organizational members to the need for change and gain their cooperation to bring about the change.[9]

Communication Plan

A vital element in motivating people to change is the effective communication between the change managers and the stakeholders impacted by the change. Lack of and insufficient communication is one of the main reasons why change efforts fail. Change management experts note that selecting the appropriate method for communication, as well as deciding on the content of the communication, are extremely important.[12] In addition to using a formal communication plan to communicate, change managers must engage the different stakeholders in an open dialogue about the change and allow them to state their views and to provide feedback into the change process. Frequent communications are important during the planning and implementation stages, as this helps to alleviate employee fears and begins to build support for the change. Change managers can utilize existing and regular forms of communication, such as newsletters, web sites, meetings, etc to get the message out.

Change Implementation Strategy

A change strategy is a critical component of any offshore outsourcing initiative. To develop an effective strategy, change managers must determine the long term goals and objectives of the offshore outsourcing effort. By encouraging the involvement of the middle management and non-managerial level employees in this strategy development process, their buy-in can be created from the very start.

Teamwork

In order to create buy-in from the employees early in the change process, the change management team should consider creating and leading cross-functional working groups, comprised of middle management and non-management level employees, to work on aspects of design and planning (tasks could include data gathering and analysis, developing new work processes, developing performance measures, etc.). In so doing, the change managers empower these groups to act on the change and signal to them that their input is considered important, thereby reducing resistance to the change.

Education and Training

A key element of change management is the identification of the education and training needs of the organization with a view to develop new competencies (knowledge, skills, and attitudes) for managing the transition to the desired state. To better manage offshore initiatives, change managers can develop a training curriculum for employees who will be retrained in the new competencies and the training should include topics, such as vendor relationship management, cross-cultural communication, contract management, vendor performance monitoring, and conflict management.

Pilot Projects

Change managers must consider introducing large scale changes, such as offshore outsourcing, gradually through small projects. Pilot projects provide the opportunity to test one or more of the alternative approaches to offshore outsourcing, thus offering valuable lessons for further implementation. Moreover, they are less risky and successful pilot projects can stimulate interest in larger-scale projects. Change managers should highly publicize and even reward success from pilot projects in order to reinforce new behaviors.[7]

Performance Monitoring

Setting up clear measures of performance is vital to the process of managing change. The performance measures should focus on reviewing the effects of the change through systematic information gathering and analysis. A good monitoring system combines elements of both quantitative and qualitative measures to produce timely information about progress toward stated goals and can help detect potential problems before they arrive.

Concludes on page 34.

Job Roles and Organizational Design

As an organization considers offshore outsourcing, change managers must identify affected roles and develop new roles and organizational structures for ensuring ongoing management and oversight of offshored activities. It is important to clearly define and communicate the new roles and integrate them into the organization's performance management system. It is equally important to distinguish the roles and responsibilities between internal and offshore staff. In many cases, the role of the internal staff may be enhanced by shifting their focus to business issues, user interactions, and vendor relationship management.

Rewards and Recognition

One way to promote offshore outsourcing is by aligning the rewards and recognition programs to the new behaviors needed to institutionalize the change. Change experts state that by aligning the rewards and recognition structure, senior management can exhibit strong visible signs that the organization actually values what it claims to value.[13] The change management team can formally recognize individuals and teams in a public manner for their contributions and for demonstrating new behaviors. In addition, extrinsic rewards, such as cash, gifts, and pay increases, can be provided to acknowledge desired new behaviors. For those who are intrinsically motivated, intrinsic rewards should be implemented to further increase their participation.

Continuous Improvement

Change managers can play an important role in supporting a continuous improvement culture following a change. A continual improvement mindset can enable organizations to look for new ways to improve their offshored business processes through small incremental changes, thus generating improvements in efficiency and overall organizational performance.

Conclusion

With the growing globalization of the world economy, an increasing number of firms are using offshore outsourcing as a strategic tool to deal with cost pressures and rapidly changing market conditions. However, adapting to changes related to offshore outsourcing has been complex and challenging for firms to achieve due to various barriers, including differences in language and style of communication, working methods, organizational culture, and internal employee resistance to change. Overcoming these obstacles and capturing the benefits of offshore outsourcing requires firms to undertake well planned and executed change management programs. While ineffective change management can negatively impact a firm's competitive advantage in the market place, effective change management can positively impact the firm's profitability and shareholder value.

References

1. PhRMA, Pharmaceutical Industry Profile 2008, Washington, D.C.: Pharmaceutical Research and Manufacturers of America, 2008.
2. Bloch, M., Dhankhar, A., and Narayanan, S., "Pharma Leaps Offshore," *The McKinsey Quarterly,* July, 2006.
3. NelsonHall, BPO Opportunities in Healthcare and Pharmaceuticals Sector in 2009, Bracknell, United Kingdom: NelsonHall, p. 79.
4. Aiken, C. and Keller, S., "The Irrational Side of Change Management," *The McKinsey Quarterly,* April, 2009.
5. Beer, M. and Nohria, N., "Cracking the Code of Change," *Harvard Business Review,* May-June, 2000, pp. 133-141.
6. Farrell, D., Laboissiere, M.A., and Rosenfeld, J., "Sizing the Emerging Global Labor Market: Rational Behavior from Both Companies and Countries Can Help it Work More Efficiently," *The Academy of Management Perspectives,* Vol. 20, No. 4, 2006, pp. 23-34.
7. McNish, M., "Guidelines for Managing Change: A Study of Their Effects on the Implementation of New Information Technology Projects in Organizations," *Journal of Change Management,* Vol. 2, No. 3, 2002, pp. 201-211.
8. Khong, K.W., "The Perceived Impact of Successful Outsourcing on Customer Service Management," *Supply Chain Management: An International Journal,* Vol. 10, No. 5, 2005, pp. 402-411.
9. Kotter, J., **Leading Change,** 1st Ed., Cambridge, Massachusetts: Harvard Business School Press, 1996, p. 187.
10. Dobson, D., "Big Change Programs: Increasing the Likelihood of Success," *Journal of Change Management,* Vol. 2, No. 1, 2001, pp. 7-22.
11. Pitt, L., Murgolo-Poore, M., and Dix, S., "Changing Change Management: The Intranet as Catalyst," *Journal of Change Management,* Vol. 2, No. 2, 2001, pp. 106-114.
12. Goodman, J. and Truss, C., "The Medium and the Message: Communicating Effectively During a Major Change Initiative," *Journal of Change Management,* Vol. 4, No. 3, 2004, pp. 217-228.
13. Higgs, M. and Rowland, D., "Developing Change Leaders: Assessing the Impact of a Development Program," *Journal of Change Management,* Vol. 2, No. 1, 2001, pp. 47-64.

About the Author

T.R. Ramanathan holds a doctorate in business administration (DBA) from the Newcastle Business School at Northumbria University, United Kingdom. He obtained his MS and M.Phil. degrees in organizational dynamics from the University of Pennsylvania in Philadelphia. His research interests include organizational change, global sourcing, and IT portfolio management. He has worked for the pharmaceutical industry for more than eight years and was recently involved in managing offshore outsourcing operations for a global pharmaceutical company. He can be contacted by telephone: +1-609-433-9161 or by email: ramanathan_tr@yahoo.com

Newcastle Business School, Northumbria University, City Campus East, Newcastle-upon-Tyne NE1 8ST, United Kingdom.

Reducing the Cost of Compliance
With Risk-Based Testing of Your Balances

Adopt Good Weighing Practice™ (GWP®) into your quality management system to control your balances with minimal effort. GWP® provides all relevant testing procedures in a single document devised for auditing purposes.

- **Request your GWP® recommendation document**
- **Register for a GWP® webinar**
- **Check your weighing risk online**

www.mt.com/GWP

METTLER TOLEDO

This article discusses how to apply the GAMP 5 quality risk management strategy to maintain compliance in laboratory computerized systems.

Applied Quality Risk Management: Case Study – Laboratory Computerized Systems

by Judy Samardelis and Winnie Cappucci

Background

Risk management concepts in the healthcare industries have matured and harmonized over the years as reflected in ICH Q9 Quality Risk Management. The use of risk management is now an expectation in all aspects of our business. GAMP 5 provides guidance in applying these concepts to the development, implementation, and maintenance of computerized systems. As emphasized in both GAMP 5 and the article written by Kevin Martin and Randy Perez, GAMP 5 Quality Risk Management Approach,[1] "risk to the patient and product quality are the primary points of concern."

This article provides an actual case study that addresses the risk management of computerized systems supporting different regulated business processes. As stated in the article referenced above, "It should be possible to reduce or eliminate unwarranted work at all risk levels, but especially on low risk areas, freeing critical resources to mitigate higher risks." Thus focusing the most effort on computerized systems where failures would have the highest risk of impact to the patient, product, or business. Certainly, computerized systems supporting the release of product to market present one of the highest risks to patient safety and product quality. A simple system that generated an incorrect result for a release assay could compromise patient safety.

Case Study

General

The approach described here is not intended to be a "one-size-fits-all" recipe, but rather one example of a three-phase, five-step process for analyzing the risks associated with the use of computerized laboratory instruments in a regulated business environment. Applying risk management throughout the instrument lifecycle from concept to retirement will increase reliability and enhance patient safety and product quality.

Business risk, patient safety and product quality, data integrity, and the system's functionality are evaluated and assessed using criticality levels. The criticality levels are assigned prospectively. For those systems defined as medium or low risk, criticality should be reassessed if a functional failure of the system occurs during the validation. Tester misuse of system commands or protocol errors are not considered functional failures.

This article will present how one company developed the risk assessment of a spectrophotometer used in a development laboratory as compared to the same instrument used in a commercial manufacturing site. The outcome is based on the assigned risk definitions and attributes associated with the use of the instrument in the different areas of the business. A spectrophotometer supporting a development manufacturing run will have different risk profile than one supporting commercial manufacturing. Nevertheless, both will impact the business process and require mitigation to reduce the risk of potential safety issues. The risk-based approach facilitates scaleable validation by focusing activities on critical attributes, ensuring the validation effort will be commensurate with the overall risk of the process. Use of the instrument cannot create a greater risk than those inherent to the process supported by the instrument.

Method failures, calibration, and sample preparation are not within the scope of the case

Continued on page 38.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2009,
Vol. 29 No. 5

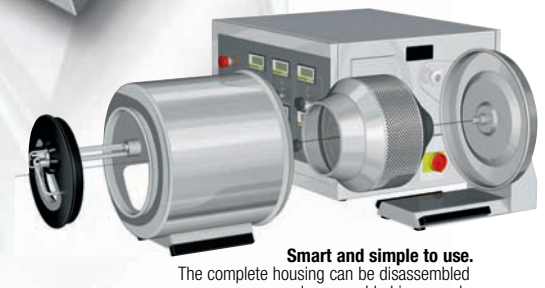
World-Class Tablet Coating in a Bench Top Tablet Coater

GMPC I Mini-Coater

The new GMPC I Mini-Coater makes world-class coating results possible for extremely small batch sizes of 500-2000 g.

With the new Mini-Coater system, you can achieve superior coating at very small batch sizes, thus reducing research and development costs considerably. With three interchangeable pans, the system is extremely flexible and ready for immediate operation.

- Aqueous and solvent processing
- Plug & Play
- Optional qualification package for clinical samples
- Exceptionally attractive price



Smart and simple to use.
The complete housing can be disassembled and reassembled in seconds.

- Fluid Bed Systems
- Vertical Granulators
- Product Handling
- **Pan Coaters**
- Process and Plant Engineering
- Services

Glatt Air Techniques Inc.
20 Spear Road
Ramsey, NJ 07446 / USA
Phone: +1 201 8 25 87 00
Fax: +1 201 8 25 03 89
eMail: info@glattair.com

Glatt GmbH Process Technology
Werner-Glatt-Straße 1
79589 Binzen / Germany
Phone: +49 7621 6 64 0
Fax: +49 7621 6 47 23
eMail: info@glatt.com

www.glatt.com

Glatt®

PE / ISPE – SEPTEMBER / OCTOBER 2009 – NEUBERGER.DESIGN

"…the assignment of business risk is determined by the use or purpose of the test results in the business process. Therefore, knowledge of what the instrument test results are used for in support of the business is crucial."

Phase 1	Risk Analysis	Step 1	Defining Business Risk
		Step 2	Defining Risk to Patient Safety, Product Quality
Phase 2	Risk Evaluation	Step 3	Defining the Criticality of the Instrument Functions
Phase 3	Risk Control	Step 4	Validation and Assignment of Appropriate Controls
		Step 5	Monitoring Controls

Table A. The process flow for the three-phase, five-step process.

study described here. It is assumed that sample preparation and controls are in place and utilized. For guidance on calibration, please refer to the *GAMP Good Practice Guide on Calibration Management*.[3]

In order to achieve success, the following are prerequisites:

1. documented understanding of the fundamental business processes
2. established and accepted definitions of risk levels
3. meaningful assignment of the probabilities that undesirable events could occur
4. defined strategies for testing and mitigation

This case study will rely on the criteria used in a Quality Risk Management Process and the following five questions suggested by *GAMP 5*:[2]

1. What are the hazards or risks that could lead to harm because failure of instrument functionality? It is assumed that the instrument failure produces erroneous test results.
2. What is the impact of the failure? How critical is the instrument in the GxP process? What is the potential harm if affected products are released for use based on erroneous data, either commercially or clinically?
3. What is the probability of the failure? The impact and probability of the failure must be fully understood in the context of the business use to allow for a proper designation of high, medium, or low criticality.
4. Because probability of failure and likelihood of detection are difficult to accurately predict with a new computerized system, quantitative estimates are utilized to facilitate decisions. These assumptions can be evaluated during the validation activities.
5. Can measures be put in place to avoid the failure? Can errors from the failure be detected at other points in the business process before harm to the patient or business occurs?

Quality Risk Management Process Description

The process flow for the three-phase, five-step process is outlined in Table A.

Phase 1, Step 1 – The assignment of business risk is determined by the use or purpose of the test results in the business process. Therefore, knowledge of what the instrument test results are used for in support of the business is crucial. The business risk is assigned as high, medium, or low and is defined in Table B.

Phase 1, Step 2 – The assignment of risk to patient safety can be based on the history of the reliability and data integrity of the laboratory instrument test results if they exist. For new instruments, the manufacturer specifications can be utilized to identify functions that impact patient safety or product quality. The risk to patient safety is assigned as high, medium, or low, as described in Table C.

Business Risk Level	Definition	Additional Attributes to Consider
High	The instrument produces a result that could impact the manufacturing business process in a manner leading to significant long-term detrimental effects and/or potentially catastrophic short-term effects such as product recall or batch rejection.	- Interruption to production schedule. - No redundancy available. - Significant reduction in service level. - Complete loss of confidence on behalf of the customer. - Environmental impact.
Medium	The instrument produces a result that could impact the manufacturing business process in a manner leading to short-to-medium-term detrimental effects, such as delay of batch release or loss of partial batches. This includes instruments used only for in-process testing and redundant systems.	- Business adjustments to laboratory operations required, preventing interruption to production schedule. For example, overtime, third party contracts. - Cost of redundancy is significant, e.g., back up/replacement systems, contract laboratory, etc. - Unavailability of the system will significantly reduce the level of service and/or customer satisfaction.
Low	The instrument produces a result that has no substantial effect on the manufacturing business process. The analyst has the ability to perform a repeat of the assay without loss of product or significant delay or system is not used for product testing.	- No impact to production schedule. - System redundancy is available. - No legal liability. - Unavailability of the system will cause no or minimal interruption to service and/or customer dissatisfaction.

Table B. Business risk.

Continued on page 40.

Important technological advances are brewing in the biopharmaceutical industry…

…and advanced high-purity solutions from MKS are behind many of them.

MKS Instruments, a global leader in critical process management and control, develops and manufactures a wide range of products used in today's most sensitive biotech and biopharmaceutical processes. From instruments to control pressure and flow, to ozone generators for sterilization, to stainless steel fittings, filter housings and housing heaters, MKS has the expertise and cost-effective solutions to address the needs of the most advanced bio processes. For information on these and other MKS products, visit us online at **www.mksinst.com/biopharm.**

mks
Technology for Productivity

MKS Instruments, Inc. Phone: 978.284.4000 or 800.227.8766 (USA only) www.mksinst.com/biopharm

"…utilizing the information from Steps 1 and 2, the overall business risk impact is assigned based on the business risk and the risk to patient safety and product quality."

Risk to Patient Safety, Product Quality	Definition	Additional Attributes to Consider
High	The instrument produces a result that has a direct effect on product release or is used for in-process testing to make manufacturing decisions (e.g. spectrophotometer for determining product concentration).	- Unproven technology, new to business process. - May lead to product recall. - May lead to a significant audit observation causing disruption to operations, e.g. Warning Letter, 483. - Supporting data for product quality/product decision-making.
Medium	The instrument produces a result that has an indirect effect on product release or is used for in-process testing, but not as the final release or redundancy is built into the testing (e.g., spectrophotometers used for checking standards, titrators, polarimeters, microbial identification systems).	- Proven technology, but new to the company. - Potential product impact with limited and defined effects. - Efficacy or safety not affected.
Low	The instrument produces a result that has no effect on product release or is used as a screening tool (e.g., spectrophotometers used for checking optical density of microbial cultures).	- Simple and robust systems based on proven technologies. - System error may lead to minor laboratory rework. - Data specific to make and model on system performance available.

Table C. Risk to patient safety, product quality.

Phase 1, Completion – Utilizing the information from Steps 1 and 2, the overall business risk impact is assigned based on the business risk and the risk to patient safety and product quality.

Phase 2, Step 3 – Criticality levels are assigned in Step 3 to individual or grouped instrument functions. Using the results of Phase 1 and the manufacturer specifications, the critical system functions can be identified. The definitions of high, medium, and low criticality functions are listed in Table D.

Criticality	Definition
High	Functions that have a direct impact on data integrity (e.g., general functions of the instrument are typically high criticality).
Medium	Functions that have an indirect impact on data integrity (e.g. network interface for a system that could have the software installed locally, electronic audit trails for systems that use paper records as the official GXP record).
Low	Functions that have negligible impact on data integrity (e.g., ability to save electronic data for systems that use paper records as the official record).

Table D. Criticality of instrument functions.

Likelihood of Occurrence	Definition
High	Occurrence is frequent
Medium	Occurs, but not frequently, has been experienced previously
Low	Occurrence is sufficiently low to cause comment when it happens, almost unknown.

Table E. Likelihood of occurrence.

Likelihood of Detection	Definition
High	Obvious to users, stops process
Medium	May be noticed during testing or review of results
Low	Unlikely to be noticed during normal operation or testing

Table F. Likelihood of detection.

Phase 2, Completion – A risk assessment of the critical system functions can define the initial validation testing strategy for the instrument. The testing strategy should support the mitigation of the risks resulting from instrument usage and potential failure. Residual risks may arise from any functionality that was not addressed during the validation testing or business functionality that the instrument does not provide.

Complex instruments whose technology is new or unproven or where in-house expertise with the system is limited and that have a Phase 1 risk assessment of "medium" will require the same functional risk evaluation as those with "high." It is essential that the evaluation and its outcome is documented to demonstrate that a systematic and logical approach was followed

Phase 3, Step 4 – During the validation activities of Step 4, verification and operational controls are tested. Should the execution of a test fail, the failure is evaluated based on the criticality of the associated system functionality as defined in Table D. The evaluation of the test failure includes an assessment of the likelihood of the occurrence of the failure - Table E. The criticality of the function is then plotted against the likelihood of occurrence to determine the risk classification rating of each function. The likelihood or difficulty of detection is evaluated and defined as high, medium, or low as described in Table F.

Based upon the combination of the risk classification and failure probability and detectability, a test priority is assigned. Test prioritization is used to further focus the validation activities on high risks. This process helps to define the procedural controls or modification of the instrument method to avoid the risk or increase the detectability of the failure in the future. In this process, the validation failures are evaluated to

determine if there is an actual failure in functionality versus execution of the test or test error. To repeat, tester misuse of system commands or protocol errors are not considered functional failures.

Upon completion of the validation activities and implementation of the controls used as mitigation, any residual risk associated with the instrument is assessed and documented. If the residual risk is not acceptable, additional mitigation controls may be implemented until acceptable levels of residual risk are achieved. The validation report documents the results and failures, while providing traceability and evaluation of the likelihood of occurrence and detection. Included in the report is the summary of the subsequent controls implemented to reduce the risk and a concluding residual risk assessment.

Phase 3, Step 5 – The final step of the risk management process is risk control. At a high level, risk control may be effected by:

- avoidance (for example, in the cases of new technology that, upon evaluation, is deemed to be too risky to use)
- mitigation (the approach addressed by this article)
- acceptance of the risk as-is and transfer, whereby the risk is displaced (a unique, business-critical instrument is available only from a single vendor and additional controls may therefore be needed to ensure the accuracy of the result).

Actual Risk Assessment of the Two Spectrophotometers

Here are the results of the Quality Risk Management as applied to two spectrophotometers: one used in a GxP manufacturing facility and the other in a GxP laboratory.

1. Manufacturing Floor

The instrument is used as a screening tool to measure in process product concentration. No effect on product release.

Phase 1 Risk Level of Medium

	Low	Medium	High
Business Risk		X	
Risk to Patient Safety, Product Quality		X	

Phase 2 Risk Level of High

	Low	Medium	High
Criticality of the Instrument Functions			X

Note: As described previously, if the instrument has an overall instrument impact of high, perform a functional risk assessment for each requirement listed in the functional specification document. A detailed functional risk assessment is optional for some medium impact instruments depending upon items, such as proven technology. Simple robust systems or minor rework may be required if the instrument produces erroneous data. If errors occur during validation that had not been considered, a functional assessment can occur at that time, while evaluating the impact of the failure and the potential for detection, etc.

Phase 3 Risk Level of Low

	Low	Medium	High
Likelihood of Occurrence	X		
Likelihood of Detection			X

Overall System Impact Assessment = Medium

	Low	Medium	High
Business Risk		X	
Risk to Patient Safety, Product Quality		X	
Criticality of the Instrument Functions			X
Likelihood of Occurrence	X		
Likelihood of Detection			X

2. GxP Laboratory

Used as a screening tool for checking optical density of microbial cultures. No effect on product release, not used for product testing.

Phase 1 Risk Level of Low

	Low	Medium	High
Business Risk	X		
Risk to Patient Safety, Product Quality	X		

Phase 2 Risk Level of Low

	Low	Medium	High
Criticality of the Instrument Functions	X		

Note: As described previously, if the instrument has an overall instrument impact of high, perform a functional risk assessment for each requirement listed in the functional specification document. A detailed functional risk assessment is optional for some medium impact instruments, depending

Concludes on page 43.

"Each organization must determine the criteria surrounding the use of a laboratory computerized system in the business process when defining the risk to patient safety and the business process should a failure occur."

upon items, such as proven technology. Simple robust systems or minor rework may be required if the instrument produces erroneous data. If errors occur during validation that had not been considered, a functional assessment can occur at that time, while evaluating the impact of the failure and the potential for detection, etc.

Phase 3 Risk Level of Low

	Low	Medium	High
Likelihood of Occurrence	X		
Likelihood of Detection			X

Overall System Impact Assessment = Low

	Low	Medium	High
Business Risk	X		
Risk to Patient Safety, Product Quality	X		
Criticality of the Instrument Functions	X		
Likelihood of Occurrence	X		
Likelihood of Detection			X

Summary

Each organization must determine the criteria surrounding the use of a laboratory computerized system in the business process when defining the risk to patient safety and the business process should a failure occur. Monitoring of the instrument's performance and the effectiveness of the applied controls for mitigation should occur as part of the periodic review process in accordance with the organizations' pre-determined periodic review process.

References

1. Martin, K.M. and Perez, A.R., "GAMP 5 Quality Risk Management Approach," *Pharmaceutical Engineering,* May/June 2008 Vol. 28, Number 3, pp.24-34.
2. *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems,* International Society for Pharmaceutical Engineering (ISPE), Fifth Edition, February 2008, Section 5 – Quality Risk Management, www.ispe.org.
3. *GAMP® Good Practice Guide: Calibration Management,* International Society for Pharmaceutical Engineering (ISPE), First Edition, December 2001, www.ispe.org.

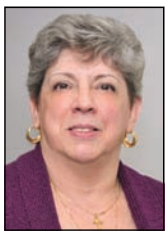
Acknowledgements

I would like to express my gratitude to the members of the GAMP Risk Management SIG and GAMP Steering Committee who reviewed and provided substantive comments during the development of this article.

About the Authors

Judy Samardelis has been in the industry more than 17 years in various roles of quality control, study director of preclinical studies, drug delivery, assay development, and validation, including several years specializing in computer and laboratory validation using GAMP® methodology in support of several Wyeth Biotech sites. In her current role, she has successfully implemented a Qualification Program for Statistical Applications using a risk-based approach as well as development of a PQ by Exception methodology to streamline validation activities. She is Co-Chair of the GAMP® Risk SIG team, member of the GAMP Steering Committee, and Co-Chair of the *Pharmaceutical Engineering* Committee. She is also a member of the GAMP® COP, PAT COP, and C&Q COP. Samardelis has a BA in microbiology from the University of New Hampshire, Durham. She can be contacted by email: SamardJ@wyeth.com.

Wyeth BioTech, 1 Burtt Rd., MS-F1100, Andover, Massachusetts 01810-5901, USA.



Winnie Cappucci has worked in the pharmaceutical industry for 40 years. She has worked as a business process owner designing and testing computerized systems for 10 years. She also worked as an IT professional with thorough knowledge of software development life cycle and computerized system operations and support for 12 years. For the last 18 years, Cappucci has worked as a quality and compliance computer validation specialist in a highly regulated environment. She has diverse software and computerized system validation and auditing experience. She is a member of the GAMP America Steering Committee and the GAMP Editorial Board. She also is a member of the PDA Industry Advisory Board for Technical Report 32 (Auditing of Suppliers Providing Computer Products and Services for Regulated Operations). She can be contacted by email: winnie.cappucci@bayer.com.

Bayer Healthcare, 6 West Belt, Wayne, New Jersey 07470-7358, USA.

... because calibration is a matter of confidence

AMETEK®
CALIBRATION INSTRUMENTS

Why AMETEK Calibration Instruments?

- **We offer a complete line of instruments for temperature, pressure, and signal calibration providing the highest accuracy and quality to optimize your process.**
- **We have more than 50 years of experience - use it!**

North American contact: Tel: +1 800 527 9999 • E-mail: cal.info@ametek.com

Worldwide contact: Tel: +45 4816 8000 • E-mail: ametek@ametek.dk

Find more info at www.jofra.com

This article will describe Building Information Modeling (BIM), provide several real-world examples of the advantages that owners have experienced when their projects were designed and developed with BIM, and offer suggestions for minimizing risks and maximizing BIM's benefits.

Enhancing Delivery of Complex Facilities with Building Information Modeling (BIM) Technology

by Andrew Signore, P.E., CPIP and Stephen R. Franey, RA

In a market that places tremendous cost, time, and performance pressures on building owners, an innovative project delivery technique could conceivably help reduce construction costs by up to 10 to 15 percent by improving constructability and reducing waste. Implementing this innovative technique also could reduce construction time for complex projects by as much as 15 to 25 percent by supporting better coordination and more organized project delivery. Building Information Modeling (BIM) technology represents a new approach to architectural and engineering design that can deliver a multitude of benefits around the delivery of complex projects, including lower first costs, compressed construction timelines, and reduced operational costs. Full-color, digital, three-dimensional models that are updated in real-time make it easier for the owner to understand and visualize the project and make decisions as an active participant on the project team. BIM's benefits don't end with the ribbon cutting, but extend throughout the project lifecycle. BIM's more robust, more accurate project documentation enables owners to operate the facility with greater clarity and continued cost savings.

This article will describe Building Information Modeling (BIM), provide several real-world examples of the advantages that owners have experienced when their projects were designed and developed with BIM, and offer suggestions for minimizing risks and maximizing BIM's benefits.

A New Approach to Architectural/Engineering Design and Construction

Project owners need speed to market and control of capital costs. The traditional way of designing, building, and delivering complex facilities – with separate silos and inherently fragmented communications – creates time and cost inefficiencies that owners can't afford. Conceived about a decade ago, BIM is a novel way of working on projects that allows coordinated, consistent information to help owners make decisions faster; provides better documentation at all levels; and enables model simulations that make it possible to predict performance prior to construction.

BIM is both a process and a design tool that provides a way to share building information among project team members through a database recognized as a 3D model. It

Continued on page 50.

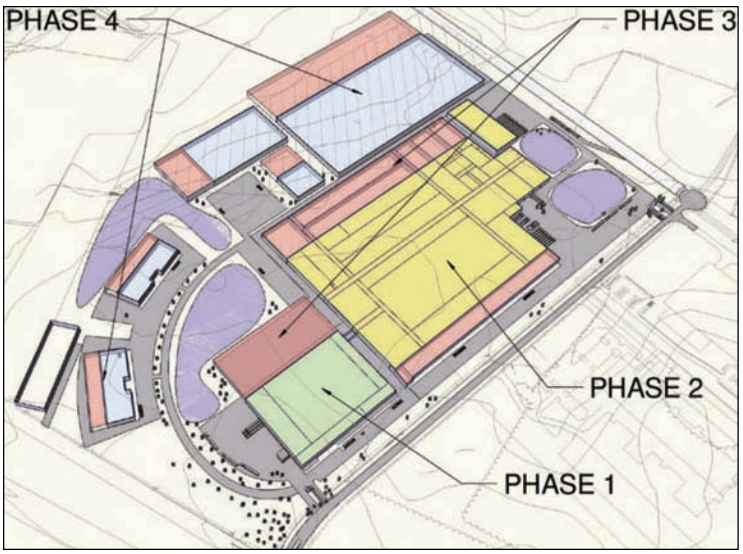
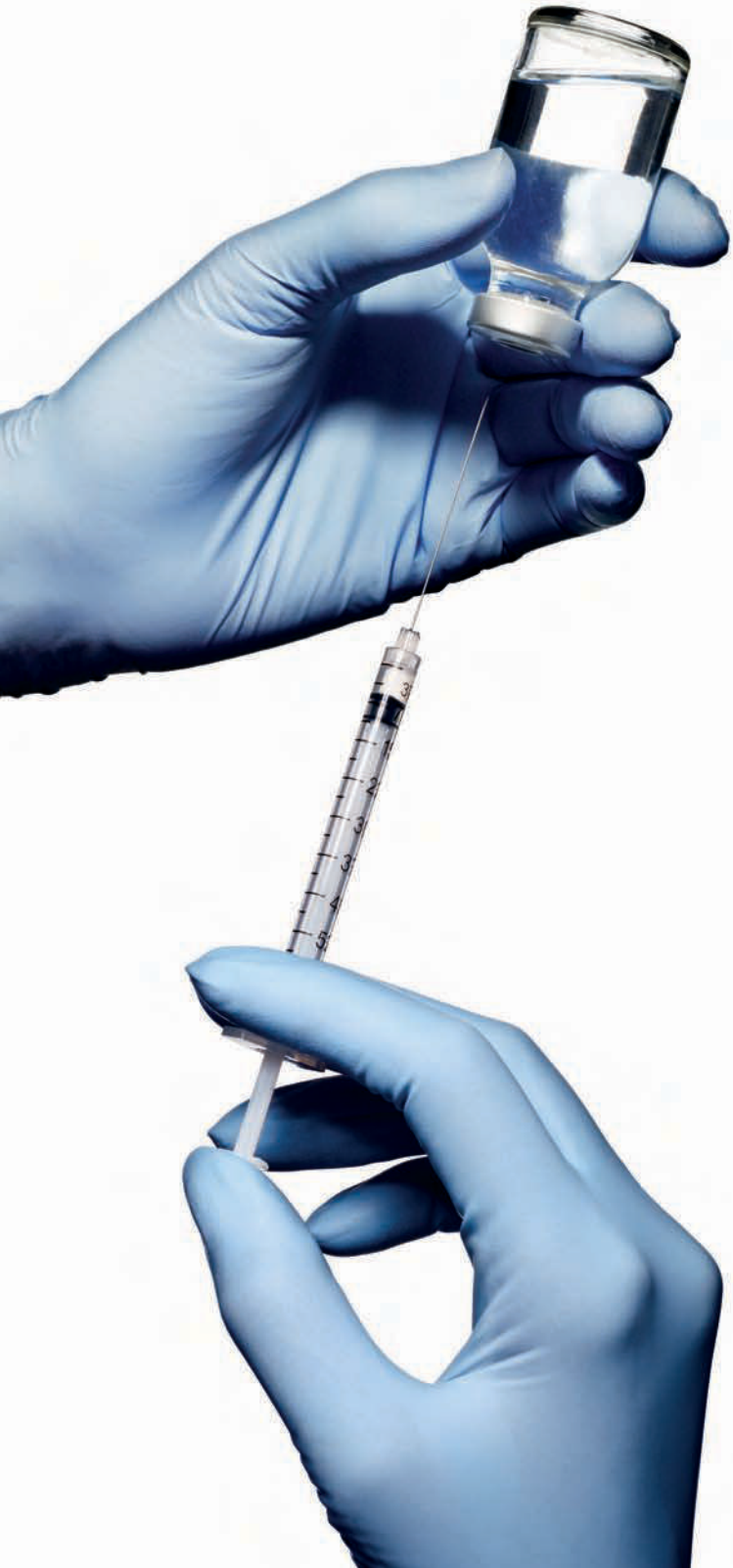


Figure 1. Multi-phased campus master planning through the use of BIM.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2009,
Vol. 29 No. 5

A healthy injection for your business



Rather than treating individual production symptoms, protect your business with:

- Comprehensive documentation packages to ensure easy validation
- Robust, reliable and repeatable performance at any scale
- Ease of cleaning and maintenance
- Minimized risk and maximized uptime

For more information or to contact a local representative visit www.alfalaval.com/biopharm

ALFA LAVAL

www.alfalaval.com/biopharm

ESE01553BEN (0307

helps the architecture, engineering, and construction (A/E/C) teams and the owners communicate more easily and clearly for better project management, coordination, and schedule integration. BIM use is growing throughout the A/E/C industry. The US General Services Administration (GSA) now requires the use of BIM for all GSA-funded capital projects. BIM software includes applications such as AutoCAD® Revit® Architecture Suite, Bentley BIM, Vectorworks Architect and ArchiCAD START. BIM organizes complex projects and improves visualization and communication for all stakeholders to a degree never before possible.

Historically, architects and engineers worked in a manually intensive environment. When Computer Aided Design (CAD) software was introduced in the early 1960s, it automated drawing tasks, but the CAD mindset still revolved around the concept of hand drafting. BIM represents the next step in the evolution of CAD. BIM technology gives designers a new level of creative control by enabling them to build a virtual 3D model. BIM combines true 3D visual studies with real-time construction documents in a single database that manages all aspects of the model. In this, BIM far outstrips the capabilities of two-dimensional CAD systems and even conventional 3D design systems, neither of which can manage a database.

BIM makes it easier to evaluate and communicate the impact of design changes, which helps minimize unexpected cost increases and construction delays. During the master-planning phase of a 76,000 square foot research and development facility, BIM enabled the design team to develop a number of alternative approaches very quickly and to communicate them with such clarity and simplicity that the owner could easily differentiate and make a decision. The designers were able to input project-related data, such as validation master planning criteria and other critical parameters, into the BIM database in parallel with the building model design.

BIM also allows the project team to explore the fourth dimension – time. For example, a team using BIM optimized construction scheduling for a new two million square foot engine assembly plant and enabled on-schedule completion of all milestones on an aggressive project schedule to meet the owner's timeline. BIM enhanced coordination among the trades by generating visually descriptive documentation that provided a better understanding of components and systems. A better understanding of component relationships can help reduce scheduling conflicts so, for example, the contractor who is installing the sprinkler isn't scheduled when the electrician is working. BIM also can be linked with Microsoft Project data.

Additionally, the designer and owner can take a "virtual walk-through" of the model. For example, it's possible to develop ergonomic studies with end users during the conceptual design phase or to check the model to make sure that end users can access valves, panel or other maintenance elements once the project is constructed. For an R&D facility in the Midwest, BIM enabled virtual laboratory development. Immersed in the virtual model, the designer and owner reviewed the space, lab equipment, casework, and utilities and made real-time changes. Using this approach on projects can streamline the design process and ultimately reduce construction confusion – leading to fewer construction delays and less rework with its associated costs.

BIM automates routine tasks, so architects and engineers can spend more time making the design more robust. Designers "build" the entire project - inside and out - from elements in a centralized project database. Many standard objects, such as "smart" 3D doors and windows, can be downloaded from their respective vendors. If the designer replaces one element with another, BIM instantly makes the change throughout the project drawings and documents, on floor plans, section views, building elevations, material schedules, etc. For highly specialized equipment, the architect/engineer also can build custom 3D objects based on vendor specifications. Vendor data is embedded within the object.

BIM's parametric capabilities and bidirectional workflow make it easier to accommodate last-minute changes to the design without significantly delaying the project schedule. "Parametric capabilities" refer to the fact that each object, such as a 3D door, in the BIM database has certain dimensional constraints associated with it that allow it to be resized. If the designer changes a dimension on a single door, BIM instantly changes the size of that specific door and simultaneously updates any associated 3D model and/or parameter information as required. Additionally, BIM's bidirectional workflow allows designers to make multiple changes at a single point in the model. If the designer changes the size of a specific door, BIM changes the size of that particular door anywhere else that it is used in the model. Together, they allow greater speed and flexibility. As a case in point, the day before the construction issue for a recent project was to be sent out, the owner wanted to extend out an exterior wall by 10 feet. The designer only had to make the change to the wall once on a floor plan drawing sheet. The model adjusted the roof, the floor, and other impacted components and automatically updated all drawing sheet views and schedules. The change was made in seconds rather than hours, as would have been the case with traditional CAD software, because the designer did not have to update each drawing sheet manually.

Additionally, team members at various geographic locations can work in the same BIM project database simultaneously. Remote users simply create a "local" file at their current location; this local file links back to the main BIM project. With real-time updates, project documents are always current. For owner and designer, this obviously saves time over having to send a single set of CAD drawings from one office to another. Smaller offices can work as if they were one large office. This arrangement is particularly beneficial for owners with complex projects that are typically too large for a single small office to handle.

BIM also gives the owner convenient access to all building information in an electronic format that is easier to search and store than dozens of boxes of documentation from the design and construction teams. The owner can use the model for future analysis and/or for projects associated with the project.

BIM Offers Operational Advantages

A BIM facility should cost the owner less to build and operate

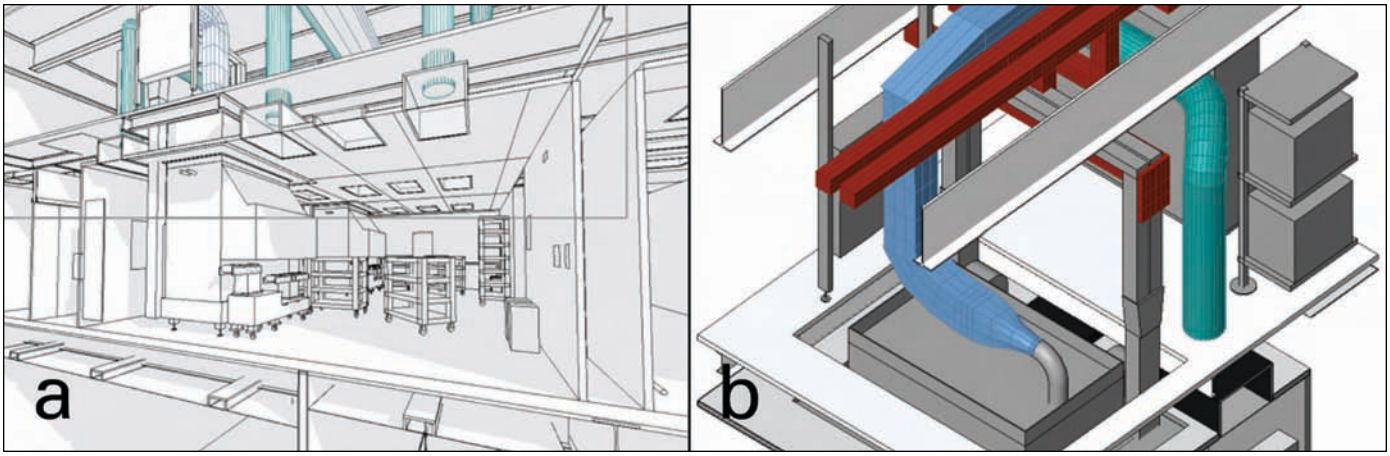


Figure 2a and 2b. BIM technology provides 2D and 3D views and allows for interference checking or "clash detection" reports.

than a conventionally designed building. For one, BIM facilitates more energy efficient design and supports analysis of building lifecycle behaviors. BIM can track utility requirements associated with each piece of material and/or equipment. The A/E professional can see all the requirements and totals for utility loads, for example, so equipment choices can be optimized during the design phase. BIM's "bill of materials" and quantitative material reports support in-house estimating teams.

Certain plug-ins make it possible to use BIM to assess whether the building meets requirements for LEED® certification by calculating the volume of sustainable materials used in construction, all driven by the project database. Used with BIM, web-based and third-party applications, such as Autodesk® Green Building Studio®, ECOTECT, and IES's Virtual Environment further analyze the building's envelope and make-up so the design team can provide solutions that best meet the owner's desire for sustainability and "green" building analysis and construction.

Owners could use model data to help reduce maintenance costs through greater accuracy and efficiency. The wealth of information in the project database can simplify record keeping and provide greater clarity regarding building components

Continued on page 52.

and system configurations. This information remains easily available to the owner, who can download it or access it via the Internet to use for facility management – like a stick-built model for the 21st century. Just as it does during the construction process, the model provides a level of visualization that facilitates everything from ordering parts to staging major upgrades, renovations, or plant shutdowns. For example, if it's necessary to pull out a chiller, the 3D model makes it possible to see exactly what equipment would have to be moved and how the area could be accessed. BIM also enables ergonomic analysis of equipment, which can provide owners with valuable information to help protect the workforce from injury.

A Different Way to Look at Things

BIM enables owners to "see" the facility long before ground is ever broken. BIM generates a three-dimensional virtual model, and not just a series of 2D representations, so it raises visualization, communication, and collaboration to new heights. Ultimately, this helps increase accuracy and reduces project costs and schedules. All members of the project team can view the BIM model remotely via the Internet, saving travel time and costs. Owners can take a virtual walk-through of the facility regardless of where in the world they are in relation to the facility, or to the design firm. BIM also provides the ability to explore "what-if" scenarios, quickly review options for architectural elements, and make changes on the fly. The designer can create camera views of interior rooms to show the owner exactly where equipment will be placed. In a research laboratory, for example, the level of detail can extend down to fume hoods, microscopes, mass spectrometers, High-Performance Liquid Chromatography (HPLC) units, sinks, etc. This capability lets the owner examine and understand ergonomic issues long before construction begins. Being able to see and compare the options in three dimensions makes it easier to make decisions.

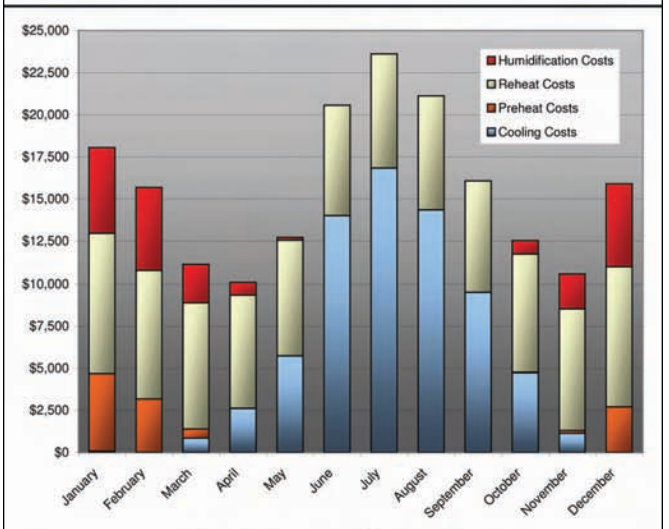
Although builders and subcontractors may be more accustomed to visualizing a finished project based on floor plans and building elevations, they benefit from BIM as well. The 3D model provides a clearer understanding of how the project comes together and helps eliminate unknowns and surprises so they can estimate costs and timelines more accurately – and often more quickly. Third-party estimating software, such as Innovaya's Visual Estimating package, allows builders to import the BIM model to generate accurate pricing and material take-offs.

BIM Technology Can Help Lower First Costs

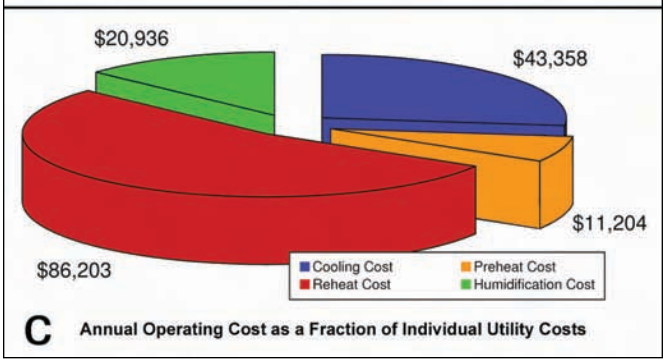
Using BIM offers several advantages, which all add up to better cost control for complex capital projects. Getting enough input to develop the model requires early decision-making and a lot of communication – which brings an exceptional level of clarity to the design process. As the model is being built, designers can use BIM to double-check to ensure that the building meets the owner's goals. For example, using parametric models of robotic assembly equipment made it possible to optimize the size of a manufacturing facility to accommodate the equipment without making it so large that it generated excessive utility costs. Reaching this degree of precision in the early stages defines the project scope much more clearly for everyone, so it is easier to keep the project team on target. When changes are required, BIM makes it easier for the owner to understand the impact of those changes – on the building

Month	Cooling Cost	Preheat Cost	Reheat Cost	Humidification Cost	Total Cost
	$	$	$	$	$
January	$23	$4,596	$8,271	$5,102	$17,993
February	$0	$3,167	$7,644	$4,870	$15,681
March	$300	$531	$7,501	$2,289	$10,620
April	$1,042	$8	$6,737	$757	$8,544
May	$2,647	$2	$6,815	$168	$9,632
June	$9,491	$0	$6,565	$0	$16,056
July	$12,115	$0	$6,784	$0	$18,900
August	$9,612	$0	$6,784	$0	$16,396
September	$5,142	$0	$6,565	$0	$11,707
October	$2,605	$38	$6,982	$794	$10,418
November	$381	$167	$7,225	$2,080	$9,853
December	$0	$2,697	$8,329	$4,874	$15,900
Total	**$43,358**	**$11,204**	**$86,203**	**$20,936**	**$161,700**

a Monthly Operating Costs per Utility



b Monthly Operational Costs as the Summation of Individual Monthly Utilities



c Annual Operating Cost as a Fraction of Individual Utility Costs

Figures 3a, 3b, and 3c. The building envelope data created by the architect is easily extracted from the model by the mechanical team for multiple energy analysis. The architect can site new buildings not only based upon traffic flow and aesthetics and optimally orient the building so as to maximize the energy performance of the building's HVAC systems in response to solar impact as well. This project involved roughly 40,000 square feet of GMP warehouse and secondary packaging space.

and its systems, as well as on costs and timelines.

It is generally accepted that a portion of building materials for any project may be wasted. Some of this waste is due to the fact that, when the project is built from conventional 2D CAD drawings, drawing sets are either inaccurate or not developed enough to show the full extent of the interaction between the various Mechanical/Electrical/Plumbing (MEP) systems. As a result, sections often need to be reworked in the field, which costs extra time and money. BIM can help reduce the need for costly and wasteful rework by helping reduce the occurrence of such surprises. BIM's ability to run "clash detection" reports identify potential conflicts between the different disciplines. Clash detection reports show potential conflict areas in the building during the design process. Unlike a CAD drawing, a BIM model alerts designers when they are trying to put ductwork where pipework needs to run. The unique 3D model shows how the finished building "works." The designer can then change the model until all conflicts are resolved. By helping reduce the amount of material that is potentially wasted, this process translates directly into cost savings. This capability can be particularly valuable for complex facilities with intensive Mechanical/Electrical/Plumbing (MEP) requirements and highly specialized equipment. BIM plug-ins exist to allow designers to check Heating/Ventilation/Air Conditioning (HVAC) volumes and calculations based on the project model.

BIM allows for more accurate cost projections, because designers can develop accurate materials schedules. Even using CAD, designers are limited by how much information they can generate and track within a given amount of time. With BIM, once the model is built, the software automatically generates sections, elevations, and floor plans. BIM also streamlines material takeoffs, and it can even integrate the design with the project schedule. Purchasing is based on real-time data.

BIM can help owners get more accurate estimates from contractors and minimize the delays and unplanned costs associated with Requests For Information (RFIs). Projects using BIM usually generate far fewer RFIs, because the necessary information is contained in the model. Builders and subcontractors do not need to keep coming back for more information, and they don't need to build in as many contingencies for unknowns. They can approach the entire process with a better understanding of the work. This tightens up everything from the bid cycle all the way through change orders, which usually follow requests for information.

The reduction in RFIs was clearly demonstrated with a highly complex manufacturing facility that was completed successfully using BIM. A project of this size (25,000 square feet) and complexity typically might involve 50 to 80 RFIs. Following the design phase, the architectural design team and the construction management team used BIM to reduce the total RFI log to approximately 10 RFIs with no change orders because all stakeholders had a clear understanding of

Continued on page 54.

what the project involved. In fact, for this owner, the project represented a record low for RFIs, rejected submittals, and change orders for a project of this size.

BIM Supports Shorter Construction Cycles

Shortening construction cycle time can sometimes offer owners strategic advantages, and it is almost always desirable in terms of cost control. Every day in the field has associated costs for supervision, construction managers, labor, trailer rentals, etc. Although BIM frontloads the project with intensive requirements in the planning stages, it can help save costs by streamlining execution. By the time construction starts, everyone on the project team should have all the information they need to proceed. Throughout construction, they can interrogate the 3D model and view the project's traditional 2D shop drawings. The ability to visualize the project in three dimensions, eliminate potential conflicts before construction starts, and understand the impact of potential changes helps all stakeholders work more closely together and supports better buy-in.

When an owner wanted a major expansion of a vaccine production facility, BIM provided the precision in-shop assembly necessary to incorporate prefabricated MEP elements, along with modular walls and ceilings, in order to save construction time. BIM made it possible to coordinate all the disciplines involved with the structural and architectural systems. Key subcontractors for HVAC, electrical, instrumentation, plumbing, and process piping were selected early and met weekly with the design team. This approach made it possible to maximize prefabrication and subcontractors were able to get right to work. Ductwork, piping, and other systems were so well coordinated that only a few post-construction field sketches were necessary. The overall MEP scope came in under budget, the approach cut nearly 10 weeks off the critical path, and the owner met the desired goal of beating its "historical best" timeline by three months – nearly 10 percent.

Maximizing the Benefits of BIM

Project owners must understand that BIM projects run differently. Clearly, BIM offers numerous benefits in terms of tighter control, shorter schedules, reduced risk, and higher return – particularly on complex projects with tight time frames. Ultimately, using BIM does not add cost to the project and the advantages can be significant. However, BIM works best when the owners have a clear vision of what they need the building to do and can convey system requirements, philosophy of operation, and goals of the facility.

Additionally, owners should be committed to making decisions earlier in the cycle than they might be accustomed to when taking a more conventional approach. The comprehensive nature of the information necessary to develop the 3D model supports better cost estimates and better scheduling, planning, management assists, clearer bid and less waste, but attaining these benefits requires a shift in the design/build process. BIM necessarily frontloads the project with more planning. It encourages owners to make decisions and answer questions earlier in the project. It also requires a collaborative atmosphere with smooth information flow. Unlike conventional design, BIM does not leave much room for "we'll figure that out later" – at least not if the owner wants to maximize the benefits of BIM.

Not all organizations are accustomed to this degree of pre-planning. The owner who will benefit the most is the one who has a firm grasp of the project scope going in and enough in-house talent to help define that scope for the designers. Owners should have a clear idea what they need for floor plans, layout, and functionality in terms of critical performance and compliance issues. Ideally, the owner also will have preselected vendors for process equipment and major systems so the facility design can be optimized around them. These goals can best be achieved when the owner's project team has enough decision-making authority to define the scope clearly during the planning phase. It is this discipline that enables the technology to generate complete construction drawings to solicit and obtain complete bids.

When circumstances limit or delay certain decisions, BIM can still offer advantages. BIM is flexible enough to accommodate indecision, but such delays result in a less complete, less well-defined model. Similarly, using BIM does not mean that designs are locked in stone or that changes can't ever be made. However, making changes after the shop drawings are generated can diminish some of the benefits of using BIM.

Due to these subtle shifts, when using BIM, it is always important to work with a company with good project management skills.

Selecting a Vendor/Partner

When considering BIM technology, it is important to remember that the benefits of using it are subject to the process, methodologies, and specifics of the project. To maximize the advantages of using BIM, project owners must select the right provider.

BIM is just a tool. In the hands of an inexperienced woodworker, the most sophisticated saw can still make bad cuts. BIM requires senior designers who have sufficient knowledge and experience of both the software applications and a deep understanding of the industry's unique needs as well as its design and constructability challenges. To use BIM successfully, the A/E professional must understand how the building needs to function and how it needs to be put together. He or she also must have access to or be able to design each of the highly specialized elements of a complex facility. That takes skill.

Training is a significant issue. Experienced, CAD-proficient designers who are familiar with construction processes can make the transition to BIM software more quickly than inexperienced personnel. Most of the software vendors offer multi-day training sessions, but becoming truly fluent in BIM can take months, even for senior designers, because BIM also requires a change workflow. In most cases, it makes sense to provide formal training to a small group of designers and allow them to gain experience by using BIM on a specific project. This cadre can then lead the BIM initiative and transfer their knowledge of the software and the processes to the rest of the organization over time. In addition, the firm may need to evaluate its information technology and infrastructure resources to optimize timely sharing of information among team members.

Concludes on page 56.

ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

PURE STEAM GENERATOR

DESIGN AND CONSTRUCTION OF PURIFIED WATER PACKAGES ♦ DOUBLE PASS REVERSE OSMOSIS ♦ R.O. + ELECTRODEIONIZATION HOT WATER SANITIZABLE ♦ ULTRAFILTRATION ♦ MULTIPLE - EFFECT DISTILLATION UNITS ♦ PURE STEAM GENERATORS ♦ STORAGE AND DISTRIBUTION LOOP ♦ COMPLETE TURN KEY PROJECTS ♦ VALIDATIONS IQ, OQ

www.elettracqua.com

The investment in high-level design talent and experience necessary to implement BIM ultimately benefits the project owners, because BIM also frees senior-level resources from the burden of overseeing draftspeople making manual changes to drawings and schedules so top design talent can spend more time doing what it does best. This is especially critical for highly complex projects, requiring the highest degree of design accuracy.

BIM requires the A/E firm to make a significant outlay in terms of both technology and personnel. Not all firms are equipped to make the necessary investment, which can run from well into five figures up to hundreds of thousands of dollars. To compensate for that investment, along with a reduction in billable hours, owners should expect a shift toward higher-cost hours or value-based fee structures for design and engineering.

Managing Risk

BIM technology is relatively new and few contracts have been written that speak to the respective responsibilities of the designer and the builder. Although risk assumption has always been a consideration, the advanced precision of the BIM model and the degree of data sharing that it involves raises some interesting issues. Current laws and legal precedents are based on clear boundaries between the designer and the builder. This is not the case with BIM. Just like when CAD was introduced 20 years ago and design/build a decade ago, BIM requires new legal contracts.

The American Institute of Architects (AIA) and Consensus DOCS have drafted several standardized contracts designed to allow all stakeholders to share the BIM project data. The documents from the two groups differ in how they address operations approaches, property insurance, additional liability coverage, and conflict resolution.

When using BIM, it is important to draft new contracts that clearly define responsibilities and apportion risk fairly. Whether starting with a standardized document or negotiating a contract from scratch, stakeholders will need to define the level of development required for each model element and determine authorized uses (i.e., analysis, cost estimating, scheduling, etc.) for the model and model elements. The contract should specify the party that will manage the model during each phase of the project. The document also should outline a protocol for addressing any conflicts or clashes that might arise in the model. Continued snags in interoperability between design disciplines can add to work flow drag and risk for sharing data. On the other hand, BIM can help minimize changes, errors, and omissions so it might reduce potential legal issues. Selecting a highly experienced BIM vendor can reduce implementation risks.

Conclusion

For owners and operators of complex facilities, BIM technology gives unprecedented control over challenging fast-track capital projects, expansions, or major renovations. During the planning phase and throughout construction, BIM provides a repository for information sharing and exchange among all stakeholders, and it also serves as a facility maintenance turnover tool. It increases accuracy and efficiency from design through purchasing and beyond, even to operator training and maintenance. In experienced hands, BIM can prove to be an exceptionally valuable project delivery tool that can help owners realize facility goals faster and more cost effectively.

References

1. American Institute of Architecture, "Building Information Modeling Protocol Exhibit," Document E202™, 2008.
2. Myers, J., "The Role of BIM in Green Design," http://www.greenbuildingcommunity.com/feature_full.php?cpfeatureid=31857&page=1, 17 November 2008 (accessed 20 November 2008).
3. Spatial Sustain, "General Motors Embraces BIM," http://www.vector1media.com, 14 February 2008 (accessed 1 December 2008).
4. Speed, V., "Strategies for Managing Risk in a New Era of Project Delivery," *Engineering News Record,* 31 March 2008, pp. L1-L4.
5. United States General Services Administration, GSA Building Information Modeling Guide Series 01 – Overview, 15 May 2007.
6. Figures 3a, 3b, and 3c, Integrated Project Services, Life Cycle Cost Analysis Report.

About the Authors

Andrew Signore, P.E., PMP, DBIA, CPIP is Co-Founder and CEO of Integrated Project Services (IPS), a full-service engineering, construction services, and compliance company. Throughout his 30 year career, he has conceived, designed, managed, and constructed a variety of manufacturing and support facilities. He is past Chairman of ISPE, past President of the ISPE Delaware Valley Chapter, and received ISPE's Distinguished Achievement Award for his many professional contributions to the Society. As an industry leader, Signore frequently lectures, publishes, and consults in areas of strategic planning, project management, and cGMP compliance. He can be contacted by telephone: +1-610-828-4090 or by email: asignore@ipsdb.com

Stephen R. Franey, RA has more than 14 years of diverse architectural and management experience. He designs and constructs a wide variety of manufacturing support and process facilities utilizing computer aided design technologies. By employing Building Information Modeling (BIM) technology to the design process, he provides 3D simulations in critical areas to limit material waste, shutdowns, and turnarounds for clients. He can be contacted by telephone: +1-610-828-4090 or by email: sfraney@ipsdb.com

Integrated Project Services (IPS), 2001 Joshua Rd., Lafayette Hill, Pennsylvania 19444, USA.

LEAN IN VALUE OUT

It's Common Knowledge at IPS

Chances are, you're already using lean practices in your production line. When it comes to capital projects, the knowledge leaders at IPS are at the forefront of Lean Project Delivery. Our team of subject matter experts and lean practitioners use Lean tools and techniques to craft innovative project delivery solutions than can dramatically reduce waste, improve operations, align with strategic business goals, and yield the maximum ROI.

To find more value in your next project – ***GO LEAN, GO IPS.***
Visit us at www.ipslean.com or contact Kimberly Goodman at 888.366.7660.

888.366.7660 | www.ipslean.com

ipslean

This article presents an innovative system for in-line process monitoring and control of freeze-drying pharmaceuticals in vials. This system is demonstrated to avoid drying failure in a wide range of operating conditions, as well as to minimize the duration of primary drying.

PAT Tools for the Optimization of the Freeze-Drying Process

by Davide Fissore, Roberto Pisano, Salvatore Velardi, Antonello Barresi, and Miquel Galan

Introduction

Freeze-drying is a process where water (or another solvent) is removed from a frozen product by sublimation. The process consists of three successive steps:

1. *Freezing*: the product to be dried is put over shelves in a chamber and its temperature is lowered so that the water (or the other solvent) is frozen. Unfortunately, not all the solvent freezes forming ice crystals, but a certain amount (sometimes significant) remains bonded to the product and must be finally desorbed. In some cases the product (the drug and the excipients) does not crystallize, but forms an amorphous glass which can retain a high amount of moisture.
2. *Primary drying*: the pressure of the chamber where the product is placed is reduced to a low value, thus causing ice sublimation. This process is carried out at very low temperatures (typically in the range -40°C to -10°C), but it requires energy that is generally supplied through the shelves.
3. *Secondary drying*: the amount of residual water, strongly bonded to the partially dried product, is reduced to a low value by using high vacuum and moderate temperatures, e.g., 20°C to 40°C. This step is required to ensure the long term preservation of the product.

Freeze-drying is widely used in the pharmaceutical industry because the low operating temperatures reduce the damages that can occur with traditional drying processes that use higher temperatures. Moreover, the freeze-dried product has a high surface area and can be easily re-hydrated. Finally, the high value of the pharmaceuticals allows for the use of a technology that can be quite expensive, because of the slow drying rate, the use of vacuum, and the high investment and operating costs. This technology has been used for many other products, including foodstuffs, because of some specific advantages that can be achieved.[1-6]

Despite the low operating temperatures, the product can be damaged even during a freeze-drying process as a consequence of a series of stresses that are applied to the molecules of the product, which can be rather labile, in the various stages of the process. Damages can occur during freezing, due to the large variation of solute concentration, of the ionic strength and eventually of pH – for which it is generally required to add cryoprotectants to the formulation. Moreover, product damages also can occur during drying. In regard to pharmaceutical products, the final appearance and reconstitution time can be strongly affected by processing. Because of the potential for damage, during primary drying the product temperature has to be carefully maintained below a limit value that is a characteristic of the product. In the case of solutes that crystallize during freezing, this maximum value corresponds to the eutectic point and product temperature has to be maintained below this value to avoid the formation of a liquid phase and the successive boiling due to the low pressure. In case of solutes that remain amorphous during freezing, the constraints are generally more demanding, as the maximum allowed product temperature is close to the glass transition temperature in order to avoid the collapse of the dried cake.[7] This value can be very low, lower than -30°C or -40°C in case of glucose, sucrose, and proteins, and is also dependent on the residual moisture. As a consequence, the constraints are active during or at the end of primary drying. The occurrence of the collapse of the dried cake, as well as of the shrinkage (that is generally due to limited and localized collapse phenomena), can be the cause of a higher residual water content

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2009,
Vol. 29 No. 5

in the final product, a higher reconstitution time, and the loss of activity of the pharmaceutical principle. Furthermore, a collapsed product is often rejected because of its unattractive physical appearance.[8,9,10]

In addition to the temperature, the residual amount of frozen water has to be monitored in order to detect the ending point of primary drying. In fact, if secondary drying is started before the end of the previous step, the product temperature may exceed the maximum allowed value, thus causing melting or collapse, while if secondary drying is delayed, the cycle is not optimized and the cost of the operation increases.

Finally, the residual water content at the end of secondary drying has to be monitored. For most products, the target level of residual water is very low, usually from less than 1.0% to 3.0%, even if for certain products it has been demonstrated that a too low level of residual water should be avoided and the final residual moisture must be in a definite range.[11]

Therefore, it is clear that in order to manage a freeze-drying process, we need an efficient monitoring and control system, as it has been recently addressed in the Guidance for Industry Process Analytical Technology (PAT) issued by the US Food and Drug Administration in September 2004. This guidance describes a regulatory framework encouraging the design and implementation of innovative pharmaceutical development, manufacturing, and quality assurance to support innovation and efficiency to have safe, effective, and affordable medicines. PAT is considered to be a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. Quality cannot be tested into products, but it should be built-in or should be by design. The benefits that can be achieved by an optimal monitoring and control policy during a freeze-drying process have been recently discussed by Sadikoglu, et al.[12]

Monitoring of primary drying is particularly difficult as it is not possible to measure in-line the parameters of interest, i.e., the product temperature and the residual water content, without interfering with the process dynamics or impairing the sterile conditions usually required when pharmaceuticals are processed. An example of widespread, but invasive monitoring device is in fact, the measurement of the product temperature obtained by inserting a thin thermocouple (in lab-scale equipment) or a resistance thermal detector (in manufacturing) inside the vial. This may alter the elementary phenomena of nucleation and ice crystal growth. For example, the vials where thermocouples are placed tend to show a lower degree of supercooling than the surrounding vials and form fewer and larger ice crystals which results in lower product resistance to mass transfer and shorter drying time in comparison to the rest of the batch. Moreover, the insertion of thin thermocouples affects the heat transfer to the product. Finally, the probe insertion compromises the sterility of the product and it is not compatible with automatic loading/un-

Continued on page 60.

loading systems used in industrial-scale freeze-dryers, even if the last problem can be solved using a wireless system.

As a consequence of these technical limitations, even the most advanced industrial freeze-dryers have control systems that are no more than data acquisition tools for certain key variables and the freeze-drying cycle is usually specified by means of a recipe in terms of shelf temperature and chamber pressure over time. These values are obtained from an extended experimental campaign based on trials and errors. However, this procedure does not guarantee repeatable conditions for freezing and sublimation steps. There can be changes from batch-to-batch due to stochastic subcooling, leading to different nucleation temperatures. Moreover, there may be further changes over time introduced by the operator or caused by variations in the materials or operating conditions. In addition, the small-scale equipment, used for recipe development, and the large-scale equipment, used in the industrial process, are different with respect to vapor fluid-dynamics, temperature distribution over the shelves, heating/cooling capacity, and radiation effects. The result is that a recipe developed in a pilot-scale freeze-dryer could result in product damage when used in an industrial-size apparatus. Therefore, it is very important to have a system that can monitor the process and undertake adequate control actions to compensate for any changes in the operating conditions or in the performance of the equipment and to allow for a reliable scale-up from the pilot-scale to the industrial-scale unit.

In this framework, the authors have been involved with several European universities and pharmaceutical companies in a European research project (LYO-PRO) with the goal of optimizing and controlling the freeze-drying of pharmaceutical proteins. Presently, the research activity at Politecnico di Torino is focused on the design of monitoring systems that couple the hardware (physical sensor) with the software (mathematical model). When monitoring a process, this provides a method to estimate reliably those variables that cannot be measured (or whose measure is expensive or time consuming). When controlling a process, this provides a method to initiate a control action that considers the effects of it in the future; therefore, optimizing the process in addition to satisfying the constraints.

This article is focused on the primary drying phase of the freeze-drying process as this step is generally recognized to be the longest and the most risky phase of the whole process. This is due to the fact that the amount of bounded water in the partially dried product is higher during primary drying; therefore, the product has to be maintained below a very low temperature. If the temperature increases, collapse (or melting) can occur. As a consequence, the duration of primary drying can be very high. On the contrary, higher temperatures are allowed during secondary drying because of the lower amount of residual moisture. Monitoring and control of secondary drying will be the subject of a future work.

The state of the art of the techniques available to monitor primary drying have been recently reviewed and discussed by Barresi, et al.,[13] where an innovative and modular monitoring system is discussed, pointing out the advantages that can be obtained by means of redundancy and synergistic effect of various devices. This system also can provide information on both the whole batch and on single vials. The end of primary drying can be effectively determined through different techniques, allowing data reconciliation and resulting in a very robust system. The measurement of product temperature and residual water content is not possible with "classical" monitoring tools, e.g., thermocouples. In order to use modern control tools that allow for process optimization and guarantee product quality, other parameters, e.g., the heat transfer coefficient between the shelf and the vials and the resistance of the dried product to vapor flow, have to be known. These variables can hardly be directly measured, but they can be estimated: a simple approach consists of perturbing the system and solving the appropriate dynamical model by fitting it to the experimental physical response to recover the unknown parameters. A well known example of this approach is the Pressure Rise Test (PRT). This article proposes an innovative algorithm, called *Dynamic Parameters Estimation* (DPE), based on the unsteady-state mass and heat balances for the product in the vials. A new predictive approach to the control is also presented, illustrating the performance of a control system developed by the authors. Results obtained in a small industrial-type apparatus (LyoBeta 25 by Telstar, Spain) with a chamber volume of 0.2 m^3 and equipped with this control software are shown to prove the effectiveness of the proposed algorithms in a wide range of operating conditions, thus, demonstrating that product damages can be avoided even when the process becomes mass-transfer controlled and when the operating pressure is suddenly changed.

Process Monitoring: DPE Algorithm

Non-invasive monitoring techniques have been proposed in the past. Most of these techniques use the in-line measure of the pressure rise occurring when the valve placed between the drying chamber and the condenser is closed for a short time (typically from five to 30 seconds) and estimate the temperature of the sublimating interface and other parameters, using a mathematical model of the process. Several algorithms were proposed in the past to interpret the PRT, namely the Barometric Temperature Measurement,[4,5,14] the Manometric Temperature Measurement,[15-18] the Dynamic Pressure Rise,[19] and the Pressure Rise Analysis.[20-22] What differentiates one method from the others is the type and the detail of the mathematical model used and the parameters that are estimated. In fact, some of the previous approaches are based on the sum of elementary mechanisms or rely on simplifications. The sublimation flux of the solvent can be calculated from the same mathematical model used to fit the curve of pressure rise or from the slope of the curve of pressure rise at the beginning of the test: the two procedures give of course similar results and this can be used as a consistency check. By performing some PRTs throughout primary drying, it is possible to evaluate the evolution of the product temperature, and by integrating the solvent flux, it is possible to calculate the residual ice content of the solid, thus, detecting the ending point of the primary drying.

The *Dynamic Parameters Estimation* (DPE) algorithm is an advanced tool proposed by Velardi, et al.,[13,23] to interpret the results of the PRT in a more reliable way: it implements an unsteady-state model for mass transfer in the drying chamber and heat transfer in the product, given by a set of partial differential equations describing:

- conduction and accumulation of heat in the frozen layer of the product
- mass accumulation in the drying chamber during the PRT
- time evolution of product thickness

The details of the model can be found in Velardi, et al.,[23] and in Barresi, et al.,[13] and are summarized in Annex 1. The system of equations is integrated in time in the internal loop of a curvilinear regression analysis: the cost function to minimize in a least square sense is the difference between the simulated values of the pressure in the drying chamber and the actual values measured during the PRT. The parameters that are estimated are the temperature of the sublimating interface at the beginning of the PRT and the mass transfer resistance to vapor flow in the dried layer. Beside these, other results are available:

- the temperature profile of the product at any axial position (and thus at the product bottom) at each time during the PRT
- the heat transfer coefficient between the heating shelf and the vial
- the actual thickness of the frozen portion of the product
- the solvent sublimation flux in the drying chamber
- the estimation of the time required to complete primary drying

These measurements are not made continuously, but on a timely basis, typically every 30 to 60 minutes. An example of the results that can be obtained when the DPE algorithm is used to monitor a freeze-drying cycle as shown in Figure 1. It is possible to see that in the first part of the cycle the temperature at the bottom of the vials estimated by means of the DPE algorithm is very close to the value measured by a thermocouple placed in a vial. The earlier increase of the temperature measured by the thermocouple is due to the fact that the sublimation rate is generally higher in the monitored vial with respect to the other vials of the batch; therefore, the primary drying is completed early. The ratio of the signals of a capacitance manometer and of a thermal conductivity gauge, like the Pirani gauge, is used to asses the end of primary drying. At that point, the concentration of water into the drying chamber becomes very low; thus, the pressure measured by Pirani (that is generally calibrated for air) approaches that measured by the capacitive gauge.[24] This method has been used in this case to verify independently the end of primary drying, even if the Pirani gauge is not generally used in production

Continued on page 62.

plants because it suffers steam sterilization. New models of the Pirani gauge, using nickel or platinum for the filament rather than the standard tungsten, can cope with several sterilization cycles.

The estimated product temperature decreases nearby the end-point: similar results also have been obtained with the other algorithms based on the PRT. One of the proposed causes to explain this is that when primary drying is approaching the end, a fraction of the vials (mainly the edge-vials, because of radiation from the chamber walls) has already finished sublimating, while DPE continues interpreting pressure rise curves assuming batch uniformity or rather a constant number of sublimating vials. A decrease in pressure rise, corresponding to a lower sublimation rate, may be interpreted by the algorithm as a reduction of the front temperature. As a consequence, the monitoring methods based on the PRT cannot be used in the last part of primary drying. The DPE algorithm is based on a much more detailed model of the drying; the result is that the estimations can be consistent for a large fraction of the primary drying. Moreover, the DPE algorithm could be modified in order to take into account in some way the batch heterogeneity.[25] In any case, care must be given when information obtained using monitoring methods based on the PRT is used to control the process. In fact, all these algorithms estimate the mean value of the product temperature, but in some vials (e.g., those placed at the edges of the tray) product temperature can be higher. This has to be taken into account when setting the target temperature in order to avoid drying failure in those vials; this issue will be addressed in the following discussion.

Process Control

The control system for a freeze-drying process should guar-

Annex 1. DPE Algorithm

During the PRT heat transfer in the frozen layer is described by the following equations:

$$\frac{\partial T}{\partial t} = \frac{k_f}{\rho_f c_{p,f}} \frac{\partial^2 T}{\partial z^2} \quad \text{for } t > t_0,\ 0 \le z \le L_f \tag{A1}$$

$$T\big|_{t=0} = T_{i0} + \frac{z}{k_f} \Delta H_s \left(\frac{k_1 M_w}{R T_{i0}}\right)\left(\frac{p_{w,i0} - p_{w,c0}}{L - L_f}\right) \quad \text{for } 0 \le z \le L_f \tag{A2}$$

$$k_f \left.\frac{\partial T}{\partial z}\right|_{z=0} = \Delta H_s \left(\frac{k_1 M_w}{R T_i}\right)\left(\frac{p_{w,i} - p_{w,c}}{L - L_f}\right) \quad \text{for } t \ge t_0 \tag{A3}$$

$$k_f \left.\frac{\partial T}{\partial z}\right|_{z=L_f} = K_v (T_{fluid} - T_B) \quad \text{for } t \ge t_0 \tag{A4}$$

Thermodynamic equilibrium is assumed at the sublimating front, corresponding to the axial position $z = 0$. The heat fluxes at $z = 0$ and at $z = L_f$, corresponding to the internal bottom of the vial, are generally not equal during the PRT, because of accumulation in the frozen layer, except at the beginning because of the pseudo-stationary hypothesis. Thanks to this assumption, the expression for the heat transfer coefficient, K_v, assumed constant during the PRT, can be derived by equating the boundary conditions (A3) and (A4), both taken at $t = t_0$. Thus:

$$k_f = \left[\frac{T_{fluid} - T_{i0}}{\Delta H_s \left(\frac{k_1 M_w}{R T_{i0}}\right)\left(\frac{p_{w,i0} - p_{w,c0}}{L - L_f}\right)} - \frac{L_f}{k_f}\right]^{-1} \tag{A5}$$

The previous equations are completed with the equation providing the dynamics of the water vapor pressure rise in the chamber, which consists in the material balance for the vapor flowing into the chamber environment. Applying the ideal gas law and rewriting the mass flow rates as functions of the pressure driving force between the interface and the chamber, it follows:

$$\left(\frac{M_w V_c}{R T_c}\right) \cdot \frac{dp_{w,c}}{dt} = N_v A \frac{k_1 M_w}{R T_i} \frac{p_{w,i} - p_{w,c}}{L - L_f} \tag{A6}$$

Finally the total pressure can be calculated taking into account a constant leakage in the chamber:

$$P_c = p_w + p_{in} = p_w + F_{leak} t + P_{in0} \quad \text{for } t \ge t_0 \tag{A7}$$

$$P_w\big|_{t=0} = p_{c0} - P_{in0} \quad \text{for } t = t_0 \tag{A8}$$

If the value of the chamber temperature T_c is not available, it can be substituted with the product temperature at the interface of sublimation, usually committing a small error.

The actual thickness of the frozen layer is determined through a material balance written across the moving interface, which is solved contemporaneously to the previous equations. The water vapor flow rate at the interface is equal to the difference between the rate of disappearance of the frozen mass and the rate of formation of the dried mass, according to the following equation:

$$\dot{m}_w = N_v \left(\rho_f A \frac{dL_f}{dt} - \rho_d A \frac{dL_f}{dt}\right) \tag{A9}$$

The material balance at the interface can be integrated in time between the previous PRT and the actual one, obtaining:

$$L_f = L_f^{(-1)} - \frac{M_w}{R \Delta\rho} \int_{t_0^{(-1)}}^{t_0} \left(\frac{k_1}{T_i} \frac{p_{w,i} - p_{w,c}}{L - L_f}\right) dt \tag{A10}$$

where $\Delta\rho = \rho_f - \rho_d$, and the superscript "(-1)" refers to quantities calculated or measured in the previous PRT. The integral on the right hand side can be solved applying the trapezoidal rule of integration:

$$L_f = L_f^{(-1)} - \frac{M_w}{R \Delta\rho} \left[\left(\frac{k_1}{T_{i0}} \frac{p_{w,i0} - p_{w,c0}}{L - L_f}\right) + \left(\frac{k_1^{(-1)}}{T_{i0}^{(-1)}} \frac{p_{w,i0}^{(-1)} - p_{w,c0}^{(-1)}}{L - L_f^{(-1)}}\right)\right] \cdot \frac{t_0 - t_0^{(-1)}}{2} \tag{A11}$$

antee product quality, in addition to minimizing the drying time. Various approaches have been proposed in the past to get these results; most are based on the use of a mathematical model of the process that is used to calculate off-line the optimal operating conditions, i.e., the shelf temperature and the chamber pressure to minimize the duration of the primary drying. No feedback from the real operation was available and so these control systems were not able to modify the operating conditions to compensate for unpredicted changes in the operating conditions.[26-31] Moreover, this approach requires that the model perfectly describes the dynamics of the process and that all the parameters and all the variables of the process are known; the inadequacy of the model or a different value of some parameters can result in a more or less serious failure. In addition, there are other causes of batch failure. A typical case is when freeze-drying is conducted with a loading different from usual or in a "similar" equipment. If the recipe is just a sequence of set points, calculated off-line, for the operating parameters of the freeze-dryer, the state of the product is not taken into account, and due to different heat fluxes or to the effect of a different hydrodynamics and pressure distribution in the chamber, failure can occur in some cases. Finally, some unexpected variation of the parameters set-point (e.g., pressure) can damage or at least endanger the product. Failure occurs if the recipe is not "robust enough," that is if the design space is not wide enough that the system remains inside it. The solution to the problem is a good control system that can

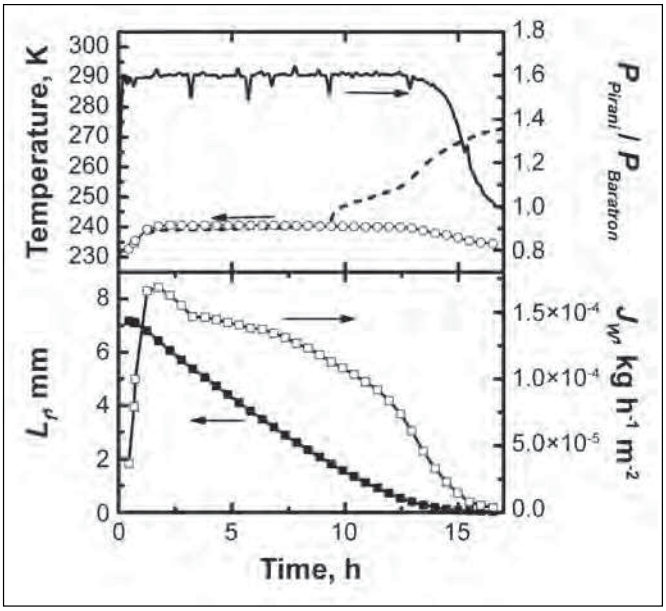


Figure 1. Example of results obtained when the DPE algorithm is used to monitor a freeze-drying cycle. Data refers to the freeze-drying of a 10% w/w sucrose aqueous solution (T_{shelf} = 265 K, P_c = 10 Pa, $d_{v,i}$ = 14.2·10^{-3} m, N_v = 175, L = 7.21·10^{-3} m). Upper graph: ratio of the pressure signals given by the Pirani and Baratron gauges (solid line), product temperature measured at the bottom of a vial (dashed line) and estimated by DPE algorithm (symbols). Lower graph: thickness of the frozen layer and sublimation flux.

Continued on page 64.

compensate for disturbances and changes in the set-up and that uses some in-line process measurements.

Some already commercially available systems use the PRT as a sensing device, e.g., Oetjen and coworkers proposed to use the results of the Barometric Temperature Measurement and a set of heuristics for the calculation of the control actions.[4,5] The use of the Manometric Temperature Measurement in a control algorithm that manipulates the shelf temperature and the chamber pressure also has been proposed and demonstrated to be a useful tool for development of a lyophilization cycle during a single freeze-drying run, but it has no predictive capacity and it cannot be used to perform a true process optimization.[32-34]

Barresi, et al.,[13,35,36] proposed to use the DPE algorithm in a control loop where the heating fluid temperature is the manipulated variable - *Figure 2*. This control algorithm uses the estimations of the product temperature, the effective heat transfer between the heating fluid and the product at the bottom of the vial, the diffusivity coefficient of the vapor in the dried layer obtained by means of DPE, some process variables (i.e., the temperature of the fluid, the pressure in the chamber, and the cooling rate of the freeze-dryer), and a simplified mathematical model for primary drying.[31] In order to run the control algorithm, the prediction horizon, which is the time throughout the algorithm estimates the evolution of the product

Annex 2. Control Algorithms

The control algorithm uses an unsteady-state model of the process which supplies the evolution of both product temperature and frozen layer thickness. The ice front position is described by Equation A12:

$$\frac{dL_f}{dt} = -\frac{1}{R_P\,(\rho_f - \rho_d)}\,(p_{w,i} - p_{w,c}) \qquad \text{(A12)}$$

The mass transfer resistance (R_p) can be calculated from the effective diffusivity of vapor in the dried layer (k_1), which can be estimated by DPE, using Equation A13:

$$R_p = \frac{RT_i}{M_w} \cdot \frac{L - L_f}{k_1} \qquad \text{(A13)}$$

Assuming pseudo-steady conditions into the frozen layer, the following relationship between L_f and the front temperature (T_i) is obtained:

$$\left(\frac{1}{K_v} + \frac{L_f}{k_f}\right)^{-1}(T_{fluid} - T_i) = \frac{\Delta H_s M_w}{RT_i}\,\frac{k_1}{L - L_f}\,(p_{w,i} - p_{w,c}) \qquad \text{(A14)}$$

The algebraic Equation A15, instead, results from the integration of the energy balance into the frozen layer and relates the interface temperature and position to the temperature at the bottom of the vial:

$$T_B = T_{fluid} - \left(\frac{1}{K_v} + \frac{L_f}{k_f}\right)^{-1}(T_{fluid} - T_i) \qquad \text{(A15)}$$

Previous equations are integrated along the prediction horizon, i.e., from the initial time (t_0) up to the horizon time (t_N) set by the User or to the time corresponding to the end of the drying (t_{N^*}); t_0 is zero at the first test and equal to the elapsed time from the first test in next runs.

If a feedback algorithm is used, the optimal heating strategy is calculated throughout the prediction horizon considering the optimal sequence of set-points of the fluid temperature as a piecewise-linear function as shown in Equation A16:

$$\begin{aligned}
&t_0 \le t < t_1 \;\rightarrow\; T_{fluid,sp,1} = T_{fluid}\,(t_0) + K_P(T_B(t_0) - T_{target})\\
&t_1 \le t < t_2 \;\rightarrow\; T_{fluid,sp,2} = T_{fluid}\,(t_1) + K_P(T_B(t_1) - T_{target})\\
&\vdots\\
&t_{N-1} \le t < t_N \;\rightarrow\; T_{fluid,sp,N} = T_{fluid}\,(t_{N-1}) + K_P(T_B(t_{N-1}) - T_{target})
\end{aligned} \qquad \text{(A16)}$$

where K_P is the proportional gain of the controller and the target temperature (T_{target}) is initially assumed equal to the maximum temperature allowed by the product (T_{max}). The design of the controller consists of determining its optimal gain according to the criterion of minimization of a particular cost function, that in this case corresponds to the Integral Square Error (ISE) as shown in Equation A17:

$$\min_{K_P}(\text{ISE}) = \min_{K_P}\int_{t_0}^{t_N}(T_B(t) - T_{target})^2 dt \qquad \text{(A17)}$$

T_B is the product temperature at the bottom of the vial and its evolution is calculated using the previous mathematical model (see Equations A12 to A15) integrated throughout the prediction horizon. It must be highlighted that the solution of Equation A17, i.e., the design of the controller, does not guarantee that product temperature remains below T_{max} because to obtain that result a constrained optimization, that is much less robust, would have been required. As a consequence, the evolution of T_B vs. time as a function of the heating policy given by the controller is evaluated (along the prediction horizon) and the possible overshoot $T_{B,max} - T_{max}$ is calculated: if this overshoot exists, then the design of the controller is repeated, assuming a lower target temperature, given by T_{max} diminished by the overshoot.

If a model-based algorithm is used, the optimal heating strategy throughout the prediction horizon is calculated as a piecewise-linear function in such a way that the bottom product temperature is maintained equal to its target. The control algorithm uses the previously described model of the process to calculate the fluid temperature needed to drive T_B to its target as faster as possible:

$$\begin{aligned}
&t_0 \le t < t_1 \;\rightarrow\; T_{fluid,sp,1} = T_{target} + (T_{target} - T_i(t_0))\left[K_v\left(\frac{1}{K_v} + \frac{L_f(t_0)}{k_f}\right) - 1\right]^{-1}\\
&t_1 \le t < t_2 \;\rightarrow\; T_{fluid,sp,2} = T_{target} + (T_{target} - T_i(t_1))\left[K_v\left(\frac{1}{K_v} + \frac{L_f(t_1)}{k_f}\right) - 1\right]^{-1}\\
&\vdots\\
&t_{N-1} \le t < t_N \;\rightarrow\; T_{fluid,sp,N} = T_{target} + (T_{target} - T_i(t_{N-1}))\left[K_v\left(\frac{1}{K_v} + \frac{L_f(t_{N-1})}{k_f}\right) - 1\right]^{-1}
\end{aligned} \qquad \text{(A18)}$$

The same considerations about the target temperature used by the feedback algorithm can be extended to the model-based controller.

temperature and computes a proper heating policy, and the control horizon, which is the time between a control action and the next one, must be set. After that, the algorithm calculates a sequence of suitable set-points for the fluid temperature ($T_{fluid,sp}$), one for each control interval along the prediction horizon, in such a way that the product temperature is as close as possible to its target. At the beginning of primary drying, when the temperature of the product is well below the upper limit, the heating fluid temperature is raised at its maximum rate compatible with the actual capacity of the equipment, and by this way, the product approaches its limit as fast as possible. After this first step, a PRT is performed and the software, using DPE algorithm, estimates the product temperature at the bottom of the vial (where the temperature is higher) over all the prediction horizon and calculates again the optimal heating policy according to the current system state. This is regularly repeated at each successive PRT so that potential mismatches between the model predictions and the actual process behavior can be taken into account. If the estimated product temperature would approach its limit, the shelf temperature is reduced in such a way that the product is maintained below its target, thus, preserving the integrity of the product.

Two control systems based on a feedback and on a model-based algorithm have been proposed and compared.[37] Annex 2 gives the details of the mathematical model used by the control algorithm. The feedback controller calculates the control action, i.e., the set-point for the temperature of the heating fluid, as a function of the difference between the bottom product temperature and the maximum allowed value. The gain of this controller is calculated in such a way that the difference between product temperature and the target value is minimized along the prediction horizon; to this purpose, a mathematical model is required to calculate the evolution of the product temperature as a function of the temperature of the heating fluid.[31] The model-based algorithm calculates

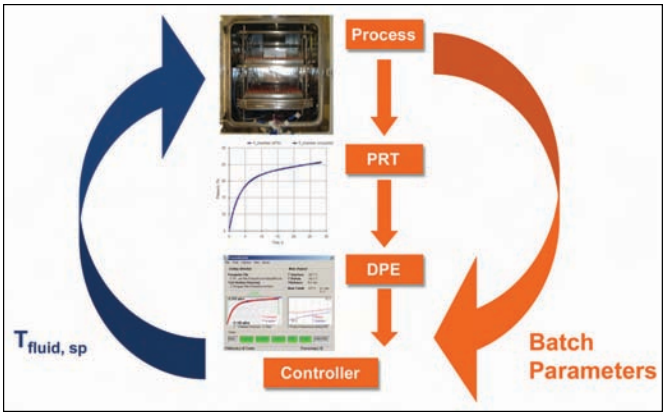


Figure 2. Operating principle of a control loop using DPE algorithm as state-estimator tool. The chamber of the equipment used for the experiments (modified LyoBeta 25 by Telstar), an example of the fitting of the PRT and a screen-plot of the parameters supplied by the system (that can be used also in simple monitoring modality) are shown.

Continued on page 66.

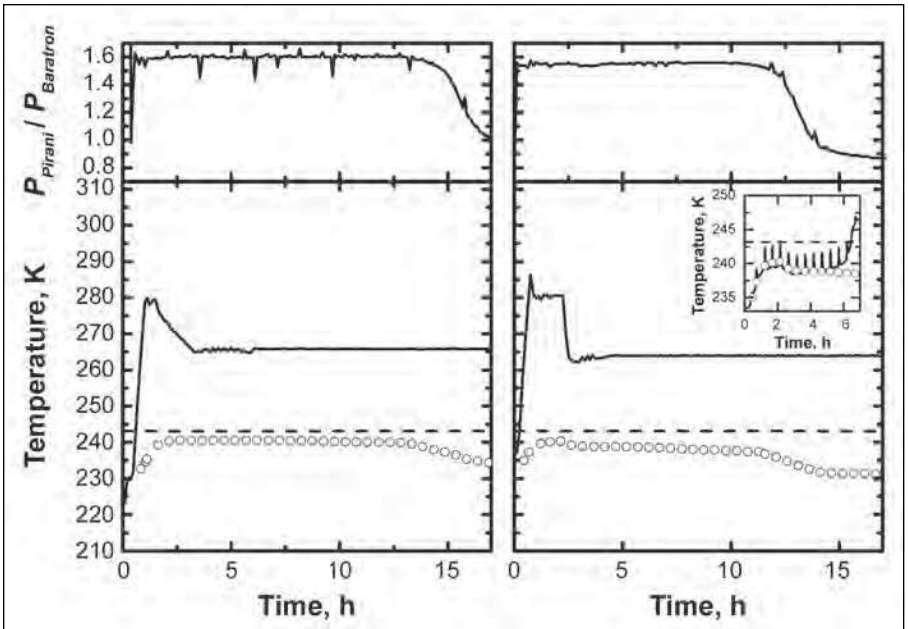


Figure 3. Examples of the application of the control algorithm to the freeze drying process of a 10% solution of sucrose ($d_{v,i}$ = 14.2•10^{-3} m, L = 7.2•10^{-3} m, P_c = 10 Pa). Results obtained using the feedback controller are shown in the left hand graph (N_v = 175), while results obtained using the model-based controller are shown in the right hand graph (N_v = 205). Upper graphs: ratio of the pressure signals given by the Pirani and Baratron gauges. Lower graphs: shelf temperature (solid line), maximum product temperature estimated by DPE (symbols) and limit temperature (-30°C, dashed line); the product temperature measured by a thermocouple is shown in the upper part of the graph on the right.

the set-point fluid temperature using the model of Velardi and Barresi[31] and imposing that the temperature of the product at the bottom of the vial is equal to the target value. The set-point of T_B is generally lower than the target temperature set by the user, corresponding to the maximum value allowed by the product, because the controller iteratively calculates a new target in order to avoid any temperature overshoot, thus, guaranteeing that product temperature is always maintained below the maximum allowed value. Moreover, the set-point of T_B is calculated taking also into account temperature rises caused by PRT. Both control algorithms take into account the actual thermal dynamics of the freeze-dryer, i.e., the actual cooling and heating rates.

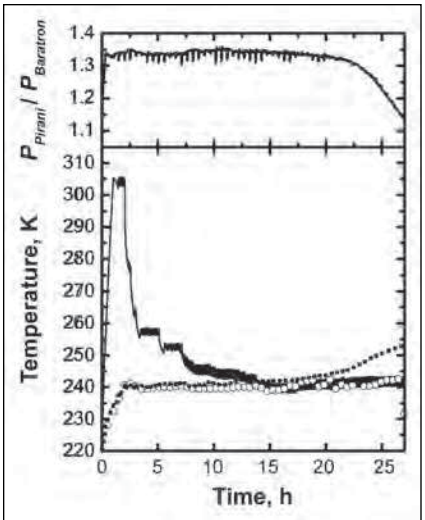


Figure 4. Example of an optimal freeze-drying cycle obtained using the model-based controller to set the fluid temperature for the freeze drying of a formulation containing 4% w/w mannitol, 1% w/w sucrose and excipients (L = 5•10^{-3} m, N_v = 132, P_c: 10 Pa, maximum allowed temperature = 240 K). Upper graph: ratio of the pressure signals given by the Pirani and Baratron gauges. Lower graph: fluid temperature (solid line), product temperature at bottom of the vial estimated by DPE (symbol) and measured through a thermocouple (dotted line).

Figure 3 shows two examples of the results that can be obtained when this control algorithm is used to control the process: the ice temperature at the bottom of the vial estimated by DPE algorithm is shown, as well as the value of the temperature of the heating fluid in case of feedback algorithm (on the left) and of model-based algorithm (on the right). It can be observed that the estimated maximum product temperature never overcomes the limit value that has been fixed, and the maximum allowable heating rate is obtained throughout all primary drying, thus, minimizing the duration of this step. The product temperature rise during a PRT is taken into account in calculating the heating policy. As a consequence, the value of the product temperature is slightly lower than the set-point, and the product temperature never overcome its limit, not even during the PRT, as it is shown by the temperature measurement given by a thermocouple placed in correspondence of the bottom of a vial. The drying time resulting when the model-based algorithm is used is slightly higher than that obtained by the feedback algorithm, but the simpler mathematical formulation (since no optimization is involved in the calculation) and the smaller computation time make the model-based approach more suitable for in-line control. It can be noted that, as discussed above, when primary drying is approaching the end, the product temperature estimated by means of

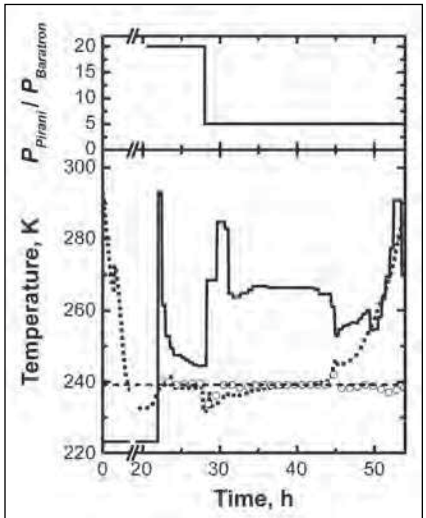


Figure 5. Example of the results obtained during a freeze-drying cycle run using the control algorithm for the primary drying stage. The batch is composed of shielded glass vials on tray (N_v = 155, L = 9.9•10^{-3} m, $d_{v,i}$ = 20.8•10^{-3} m) filled with 3 mL of a 10% w/w sucrose aqueous solution. After freezing, the chamber pressure has been set at 20 Pa and then lowered to 5 Pa after about 5 h (upper graph). The maximum allowable product temperature has been set to 240 K. The time evolution of the shelf temperature (solid line), and of the temperature at the bottom of the vials estimated using DPE algorithm (symbol) and measured by a thermocouple (dotted line) is shown in the lower graph.

DPE algorithm decreases; this behavior must be taken into account when setting the parameters of the control algorithm and in the last part of the cycle it is advisable to use the sequence of control action suggested in the previous steps, without updating it on the basis of the new (misleading) measurements. The same problem was evidenced also by Gieseler, et al.,[34] when using a different control algorithm. Oetjen and Haseley[14] proposed to use the decrease in the estimated interface temperature as an indication of end of sublimation; in any case, the end of primary drying could be reasonably estimated by extrapolating the predictions of the interface position obtained using DPE in the initial part of the run.

In both examples of Figure 3, the heat transfer from the shelf controlled the sublimation rate and the fluid temperature was usually maintained almost constant in the second part of the drying: the value of the shelf temperature assured the maximum sublimation rate since it was significantly greater than the product temperature and chamber pressure was not very influent.

In some cases, the vapor transport through the solid matrix controls the drying rate. Transition to mass transfer control may occur as a consequence of the increase of dry cake thickness, the formation of a crust, or the increase of the cake resistance during the process due to a change in its structure. There is a strong risk of failure because if the heat flux is not properly reduced, the product temperature increases. Moreover, it is very difficult to predict the occurrence of such transition. The proposed control algorithm can be effective also in this case since it guarantees the product integrity and the maximum flow rate at the operating pressure. Figure 4 shows the results obtained in a cycle where the process becomes mass-transfer controlled (after about 15 hours), as it is confirmed by the analysis of the transport coefficients estimated by the DPE algorithm. It can be observed that the fluid temperature calculated by the controller approaches the product temperature: the driving force for the heat transfer becomes very small because the constraint on the maximum temperature of the product is effective and the controller indicates that, at this moment, a reduction in the chamber pressure is convenient to increase the sublimation rate. In this case, DPE demonstrates good results up to the end of primary drying and the product temperature estimated agrees with thermocouple measurements, at least until the monitored vials are representative of the entire batch. Of course an in-line change of the chamber pressure might be useful to reduce the drying time, restoring heat transfer control.[38] Figure 5 shows the results obtained when a cycle is controlled using the previously described control algorithm and chamber pressure is changed in order to minimize the drying time when the process was approaching mass-transfer control. It is important to observe that when the pressure is decreased, the controller calculates a higher set-point for the temperature

Continued on page 68.

of the heating fluid. The result is that the temperature is maintained always close to the limit value that was previously set and the difference between the temperature of the fluid and that of the product is higher with respect to the value obtained before the pressure change. This means that the heat flux from the fluid to the product is higher, thus, resulting in a shorter drying time.

Conclusions and Future Perspectives

Results that can be obtained when a vial freeze-drying process is monitored and controlled using a new control algorithm have been shown and discussed in the article. The unique key features of this control system have been highlighted and are briefly listed below:

- uses a simple mathematical model of the drying process in order to calculate the optimal values of the shelf temperature that guarantee product quality and minimize the drying time
- uses the estimates of the state of the system and of the process parameters that are available by interpreting the PRT with the DPE algorithm and after each control time, a new DPE test is carried out and a new sequence of control actions is calculated, thus, compensating for model deviations and process disturbances
- considers the actual heating/cooling capacity of the freeze-dryer
- predicts potentially damaging temperature overshoots and anticipates accordingly the control actions
- considers temperature rises caused by PRT

Product failures can be avoided, even when the process becomes mass-transfer controlled or when the pressure in the chamber is varied. This tool appears to be an effective and efficient solution for process control in production plants, at least at relatively small scale, when it can be possible to periodically close the valve quickly. The system can be very effective also for pilot-scale units used for the initial R&D stage and it can make the passage from R&D to production scale very straightforward. To this purpose, the proposed control algorithm has been successfully tested in a pilot-scale freeze-dryer.

Further improvements can be done in the monitoring and control algorithm: in fact, control actions calculated by the algorithm are a function of some parameters (e.g., the cake resistance and the overall heat transfer coefficient between the heating/cooling fluid and the product) that can be variables among the vials of the batch. Heterogeneity of the batch is caused by radiation from chamber walls, shelves and door, the fluid-dynamics of the water vapor in the drying chamber, non-uniform temperature of the heating shelf, and non-uniform initial filling height.[39] If an aggressive control policy, based on the estimation of the "mean" state of the batch is used, a fraction of the product, whose temperature is higher, can be damaged or there can be a fraction of vials that does not satisfy the requirements because of batch heterogeneity. Thus, the control system has to cope with this occurrence. It could be possible to modify the DPE algorithm in order to take into account the variance of temperature (and of other parameters) of the batch; preliminary results have shown that this may present some difficulties.[25] Another approach consists of using the information coming from temperature measurement, coupled to a soft-sensor, in several vials.[36] Work is in progress to develop a new monitoring system that can be coupled with the control algorithm that does not require to close the valve in the spool, and this can be used in very large industrial equipment.

List of Symbols

A	cross surface of the vial, m^2
$c_{p,f}$	specific heat of the frozen layer, J $kg^{-1}K^{-1}$
$d_{v,i}$	inner diameter of the vial, m
F_{leak}	leakage rate, Pa s^{-1}
ΔHs	heat of sublimation, J kg-1
J_w	sublimation flux, kg h^{-1} m^{-2}
K_p	gain of the proportional controller
K_v	overall heat transfer coefficient, J m^{-2} s^{-1} K^{-1}
k_1	effective diffusivity of vapor in the dried layer, m^2 s^{-1}
k_f	thermal conductivity of the frozen product, J m^{-1} s^{-1} K^{-1}
L	product thickness after freezing, m
L_f	thickness of the frozen layer, m
M	molecular weight, kg $kmol^{-1}$
m	mass flow rate, kg s^{-1}
N_v	number of vials of the batch
p	partial pressure, Pa
P	total pressure, Pa
R	ideal gas constant, J $kmol^{-1}$ K^{-1}
R_p	mass transfer resistance to vapor flow in the dried layer, m s^{-1}
T	temperature, K
t	time, s
V	volume, m^3
z	axial coordinate, m

Greeks

ρ_d	effective density of the dried layer, kg m^{-3}
ρ_f	effective density of the frozen layer, kg m^{-3}

Subscripts and Superscripts

0	value at t = 0, initial time for the interval considered
(-1)	PRT before the actual one
B	vial bottom, corresponding to $z = L$
c	drying chamber
fluid	heating fluid
i	sublimating interface, corresponding to z = 0
in	inert gas
max	maximum value
shelf	heating shelf
sp	set-point
target	target value
w	water vapor

Abbreviations

DPE	Dynamic Parameters Estimation
PRT	Pressure Rise Test

References

1. Mellor, J.D., **Fundamentals of Freeze-Drying,** London: Academic Press, 1978.
2. Liapis, A.I., **Freeze Drying. Handbook of Industrial Drying** (edited by A.S. Mujumdar), Chapter 9, New York: Marcel Dekker Inc., 1987.
3. Jennings, T.A., **Lyophilization: Introduction and Basic Principles,** Boca Raton: Interpharm/CRC Press, 1999.
4. Oetjen, G.W., **Freeze-Drying,** Weinheim: Wiley-VCH, 1999.
5. Oetjen, G.W., Haseley, P., **Freeze-Drying,** 2nd Edition, Weinheim: Wiely-VHC, 2004.
6. Rey, L., May, J.C., **Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products,** New York: Marcel Dekker Inc., 2004.
7. Franks, F., **Freeze-Drying of Pharmaceuticals and Biopharmaceuticals,** Cambridge: Royal Society of Chemistry, 2007.
8. Pikal, M.J., Shah, S., "The Collapse Temperature in Freeze Drying: Dependence on Measurement Methodology and Rate of Water Removal from the Glassy Phase," *International Journal of Pharmaceutics*, Vol. 62, 1990, pp. 165-186.
9. Wang, W., "Lyophilization and Development of Solid Protein Pharmaceuticals," *International Journal of Pharmaceutics,* Vol. 203, 2000, pp. 1-60.
10. Rambhatla, S., Obert, J.P., Luthra, S., Bhugra, C., Pikal, M.J., "Cake Shrinkage during Freeze Drying: A Combined Experimental and Theoretical Study," *Pharmaceutical Development and Technology,* Vol. 1, 2005, pp. 33-40.
11. Hsu, C.C., Ward, C.A., Pearlman, R., Nguyen, H.M., Yeung, D.A., Curley, J.G., "Determining the Optimum Residual Moisture in Lyophilized Protein Pharmaceuticals," *Developments in Biological Standardization,* Vol. 74, 1992, pp. 255-271.
12. Sadikoglu, H., Ozdemir, M., Seker, M., "Freeze-Drying of Pharmaceutical Products: Research and Development Needs," *Drying Technology,* Vol. 24, 2006, pp. 849-861.
13. Barresi A.A., Pisano, R., Fissore, D. Rasetto, V., Velardi, S.A., Vallan, A., Parvis, M., Galan, M., "Monitoring of the Primary Drying of a Lyophilization Process in Vials," *Chemical Engineering and Processing,* Vol. 48, 2009, pp. 408-423.
14. Oetjen, G.W., Haseley, P., Klutsch, H., Leineweber, M., "Method for Controlling a Freeze-Drying Process," United States Patent n. 6,163,979 A1.
15. Milton, N., Pikal, M.J., Roy, M.L., Nail, S.L., "Evaluation of Manometric Temperature Measurement as a Method of Monitoring Product Temperature during Lyophilisation," *PDA Journal of Pharmaceutical Sciences,* Vol. 5, 1997, pp. 7-16.
16. Tang, X.C., Nail, S.L., Pikal, M.J., "Evaluation of Manometric Temperature Measurement, A Process Analytical Technology Tool for Freeze-Drying: Part I, Product Temperature Measurement," *AAPS Pharmaceutical Science and Technology,* Vol. 7, No. 1, 2006, article 14.
17. Tang, X.C., Nail, S.L., Pikal, M.J., "Evaluation of Manometric Temperature Measurement, A Process Analytical Technology Tool for Freeze-Drying: Part II, Measurement of Dry Layer Resistance," *AAPS Pharmaceutical Science and Technology*, Vol. 7, No. 4, 2006, article 93.
18. Tang, X.C., Nail, S.L., Pikal, M.J., "Evaluation of Manometric Temperature Measurement (MTM), A Process Analytical Technology Tool in Freeze Drying: Part III, Heat and Mass Transfer Measurement," *AAPS Pharmaceutical Science and Technology,* Vol. 7, No. 4, 2006, article 97.
19. Liapis, A.I., Sadikoglu, H., "Dynamic Pressure Rise in the Drying Chamber as a Remote Sensing Method for Monitoring the Temperature of the Product during the Primary Drying Stage of Freeze-Drying," *Drying Technology,* Vol. 16, 1998, pp. 1153-1171.
20. Chouvenc, P., Vessot, S., Andrieu, J., Vacus, P., "Optimization of the Freeze-Drying Cycle: A New Model for Pressure Rise Analysis," *Drying Technology,* Vol. 22, 2004, pp. 1577-1601.
21. Chouvenc, P., Vessot, S., Andrieu, J., Vacus, P., "Optimization of the Freeze-Drying Cycle: Adaptation of the Pressure Rise Analysis to Non-Instantaneous Isolation Valves," *PDA Journal of Pharmaceutical Science and Technology,* Vol. 5, 2005, pp. 298-309.
22. Hottot, A., Vessot, S., Andrieu, J., "Determination of Mass and Heat Transfer Parameters during Freeze-Drying Cycles of Pharmaceutical Products," *PDA Journal of Pharmaceutical Science and Technology,* Vol. 59, 2005, pp. 138-1-53.
23. Velardi, S.A., Rasetto, V., Barresi, A.A., "Dynamic Parameters Estimation Method: Advanced Manometric Temperature Measurement Approach for Freeze-Drying Monitoring of Pharmaceutical Solutions," *Industrial and Engineering Chemistry Research,* Vol. 47, pp. 8445-8457.
24. Armstrong, J.G., "Use of the Capacitance Manometer Gauge in Vacuum Freeze-Drying," *Journal of the Parenteral Drug Association,* Vol. 34, 1980, pp. 473-483.
25. Rasetto, V., Marchisio, D.L., Fissore, D., Barresi, A.A., "Model-Based Monitoring of a Non-Uniform Batch in a Freeze-Drying Process," Proceedings of 18th European Symposium on Computer Aided Process Engineering – ESCAPE18 (edited by B. Braunschweig, X. Joulia), 1-4 June, 2008, Lyon, France. Computer-Aided Chemical Engineering, 25, Paper FP_00210, CD Edition. Amsterdam: Elsevier.
26. Liapis, A.I., Litchfield, R.J., "Optimal Control of a Freeze Dryer – I. Theoretical Development and Quasi Steady-State Analysis," *Chemical Engineering Science,* Vol. 34, 1979, pp. 975-981.
27. Lombraña, J.I., Diaz, J.M., "Heat Programming to Improve Efficiency in a Batch Freeze-Dryer," *Chemical Engineering Journal,* Vol. 35, 1987, pp. B23-B30.
28. Lombraña, J.I., Diaz, J.M., "Coupled Vacuum and Heating Power Control for Freeze-Drying Time Reduction of Solutions in Phials," *Vacuum,* Vol. 37, 1987, pp. 473-476.
29. Sadikoglu, H., Ozdemir, M., Seker, M., "Optimal Control of the Primary Drying Stage of Freeze Drying of Solutions in Vials using Variational Calculus," *Drying Technology,* Vol. 21, 2003, pp. 1307-1331.
30. Fissore, D., Velardi, S.A., Barresi, A.A., "In-line Control of a Freeze-Drying Process in Vial," *Drying Technology,* Vol. 26, 2008, pp. 685-694.
31. Velardi, S.A., Barresi, A.A., "Development of Simplified Models for the Freeze-Drying Process and Investigation of the Optimal Operating Conditions," *Chemical Engineering Research and Design,* Vol. 86, 2008, pp. 9-22.
32. Tang, X.C., Nail, S.L., Pikal, M.J., "Freeze-Drying Process Design by Manometric Temperature Measurement: Design of a Smart Freeze-Dryer," *Pharmaceutical Research,* Vol. 22, 2005, pp. 685-700.
33. Pikal, M.J., Tang, X., Nail, S.L., "Automated Process Control using Manometric Temperature Measurement," United States Patent n. 6,971,187 B1.
34. Gieseler, H., Kramer, T., Pikal, M.J., "Use of Manometric Temperature Measurement (MTM) and SMART™ Freeze

Concludes on page 70.

Dryer Technology for Development of an Optimized Freeze-Drying Cycle," Journal of Pharmaceutical Sciences, Vol. 96, 2007, pp. 3402–3418.
35. Velardi, S.A., Barresi A.A., "Method and System for Controlling a Freeze Drying Process," European Patent application PCT /EP2007/059921 (19/09/2007), 2007.
36. Barresi, A.A., Velardi, S.A., Pisano, R., Rasetto, V., Vallan, A., Galan, M., "In-line Control of the Lyophilization Process. A Gentle PAT Approach using Software Sensors," *International Journal of Refrigeration,* Vol. 32, pp. 1003-1014.
37. Pisano, R., Fissore, D., Velardi, S., Barresi, A.A., "Control of Freeze-Drying Processes of Pharmaceuticals in Industrial Apparatus," *Journal of Pharmaceutical Sciences,* Submitted.
38. Fissore, D., Pisano, R., Barresi, A.A., "On the Design of on In-line Control System for a Vial Freeze-Drying Process: The Role of Chamber Pressure," *Chemical Product and Process Modeling,* Vol. 4, article 9.
39. Barresi A.A., Pisano R., Rasetto V., Fissore D., Galan, M., "Model-Based Monitoring and Controlling of Industrial Freeze-Drying Processes," Proceedings of 16th International Drying Symposium – IDS2008, Ramoji Film City (Hyderabad), India, 9-12 November, 2008, Vol. B, pp. 746-754.

About the Authors

Dr. Davide Fissore is a certified chemical engineer; he received his PhD in 2004 from the Politecnico di Torino. He has been visiting researcher at CPE-Lyon (France) and at the University of Oviedo (Spain). Currently, he is an Assistant Professor at the Department of Materials Science and Chemical Engineering of the Politecnico di Torino (Italy), teaching "Advanced Process Control." His research activity is focused on modeling, monitoring, and control of chemical processes (catalytic reactors working in unsteady-state conditions and processes of separation) and of the freeze-drying of pharmaceuticals. He authored more than 80 papers published on international journals and on proceedings of International Conferences. He can be contacted by telephone: +39-011-0904693 or by email: davide.fissore@polito.it.

Dr. Roberto Pisano is a certified chemical engineer. He received his PhD in 2009 from the Politecnico di Torino (Italy). His research activity is focused on modeling, monitoring, and control of the process of freeze-drying of pharmaceuticals. He can be contacted by telephone: +39-011-0904694 or by email: roberto.pisano@polito.it

Dr. Salvatore Velardi is a certified chemical engineer; he received his PhD in 2005 from the Politecnico di Torino. He has been visiting researcher at CPE-Lyon (France) and assistant researcher at the Politecnico di Torino (Italy). As a scientist, he has worked for DiaSorin (Italy) at the development of lab analyzers for immunological assays. For Rivoira (Praxair Italy) he is involved in the development and design of medical gas systems. He collaborates with the LyoLab research team of the Department of Materials Science and Chemical Engineering of the Politecnico di Torino; his activities include the development of new sensors for freeze-dryers, modeling, monitoring, and control of freeze-drying. He can be contacted by email: salvatore.velardi@polito.it

Professor Antonello Barresi is a certified chemical engineer; he received his PhD in 1990 from the Politecnico di Torino. He has been visiting researcher at Yale (Connecticut, US), professor at the Addis Ababa University (Ethiopia) sent by the Foreign Office as part of International Cooperation program, and "einsegnant invité" at the University of Lyon 1 (France) in 2000 and 2003. Currently, he is full professor at Politecnico di Torino, teaching "Process Design and Development," "Process Control," and "Advanced Chemical Reactors." His research activity concerns drying, mixing in homogeneous and multiphase systems, and combustion (both catalytic and homogeneous). His main research interests in drying include: drying and freeze drying of pharmaceuticals and enzymes, lyophilization of food and damaged paper documents; development of new sensors and control systems for freeze dryers, and modeling and optimization of freeze-drying. He is the author of approximately 90 papers in international journals and more than 100 conference presentations. He can be contacted by telephone: +39-011-0904658 or by email: antonello.barresi@polito.it.

Politecnico di Torino, Dipartimento di Scienza dei Materiali e Ingegneria Chimica, corso Duca degli Abruzzi 24, Torino 10129, Italy.

Miquel Galan is Director of Innovation and R&D of Telstar Lyo in Spain. He has been with Telstar for more than 24 years. He is an expert in pharmaceutical engineering, as well as vacuum technology and leak detection. He has held a position as a process engineering manager, and has managed many large freeze-drying projects. He holds degrees in chemical engineering from the Instituto Quimico de Sarria (IQS) and Industrial Engineering from the Universitat Ramon Llull. He is an active member of ISPE, PDA, and of International Society of Lyophilization - Freeze Drying (ISL-FD). He also is a member of American Society of Mechanical Engineers (ASME), The Pharmaceutical and Healthcare Sciences Society (PHSS), and American Association of Pharmaceutical Scientists (AAPS). He has chaired several freeze drying conferences and lectured on many freeze drying courses, conferences, and workshops, as well as in other topics about vacuum related subjects over the past 15 years. He can be contacted by email: mgalan@telstar.eu.

Telstar-Lyo, J. Tapiolas 120, 08226 Terrassa, Spain.

Customize Your ISPE Email!

Now you can specify your email settings and get the type of email you want from ISPE. Update your Member profile and tell us:

- Your Areas of Interest
- From which groups within ISPE you would like to receive email
- Alternative contact information in case you relocate or change jobs

Remember, your ISPE membership is "portable" and goes with you wherever you work in the industry.

To customize your settings, go online and update your ISPE Member Profile at www.ISPE.org/emailpreferences

Thank you for making ISPE your Society of Choice!

ENGINEERING PHARMACEUTICAL INNOVATION

ISPE

www.ISPE.org/emailpreferences

Early Bird Ends 12 October

Don't Miss

The Event Of The Year!

Prestigious Keynote Presenters:

- **Samuel Bogoch MD, PhD**
  Replikins, Ltd.
- **Lembit Rägo MD**
  Coordinator, Quality Assurance and Safety: Medicines Essential Medicines and Pharmaceutical Policies at the World Health Organization (WHO)
- **Antonio J. Ricco, PhD**
  Chief Technologist for Small Payloads and Instrumentation in NASA Ames Research Center's Small Spacecraft Division

Eleven Session Tracks:

- Product development
- Facilities and equipment
- Information systems
- Supply chain management
- Production systems
- Regulatory compliance
- Quality systems
- Project management
- Investigational products
- Suppliers
- Survival-focused

ISPE09 Annual Meeting

Thriving In A Survival Environment

8 • 11 November

Manchester Grand Hyatt San Diego
San Diego, California, USA

www.ISPE.org/annualmeeting

Exhibit and Sponsorship Opportunities Available

This article presents new developments in global sourcing logistics and demonstrates how pharmaceutical producers can build an integrated supply and product development strategy.

Building a Flexible, Cost-Efficient Global Supply Chain

by Simon Kaye

Global sourcing in the $500 billion world wide pharmaceutical industry is driven by far more than a temporary search for low cost. It's in fact a long-term systemic trend that necessitates rebuilding of supply chain logistics from the ground up. Building an international logistics system for manufacturers' sourcing needs today requires a quantum leap from past shipping practices, which had grown during decades of relatively stable sourcing and supply trends. The elements that make up the logistics paradigm are constantly changing, and pharmaceutical producers must have a constant awareness of those changes integrated into their total product planning process.

There is too often a notable lack of communication within major manufacturers in all industries, including pharmaceuticals, on concerns that relate to transportation. When a new product idea is conceptualized, researched, and tested, the process involved is detailed and standardized. And when the point of commercializing a new product is reached, producers consider and evaluate the packaging, the marketing, distribution and sales, public relations and advertising. However, transportation and the logistics of the supply chain are taken into account late in the game – if they are ever considered at all. Yet failing to investigate and consider the latest developments in vital logistics factors – shipping trends, customs regulations, and security requirements – can dramatically increase supply difficulties and overall costs for any product, no matter how great its potential demand.

This article will provide a proactive review of behind-the-scenes factors in pharmaceutical logistics as they relate to global sourcing. By examining regulatory requirements and practical business considerations – such as selecting the right freight forwarding partner and specifying the proper shipping terms – we will illustrate the importance of considering the latest developments right from the start to build an effective, integrated supply and product development strategy.

Regulatory Concerns

Pharmaceutical production was born in the pharmacy, but as drug production became a factory process its transport logistics became far more complex. Guidelines established by the US Food and Drug Administration (FDA), the European Medicines Agency, and other regulators for current Good Manufacturing Practice (cGMP) in the production of pharmaceuticals include requirements as they affect raw materials, in-process goods, packaging, labeling and finished goods as well as the manufacturing, testing, documentation, and product release processes. The production of pharmaceutical products requires validating for the FDA every aspect of the receiving, analysis, storage, and handling of drug actives, excipients, and other raw materials. And ensuring cGMP compliance to those standards must be integrated with the normal considerations between supplier and manufacturer. These include demand forecasting, stock levels, production plans, maximum and minimum inventory levels, reorder points, and order quantities.

The supply chain needs for pharmaceutical manufacturing are both complex and delicate, going beyond mere efficiency to require total quality in handling and care. Pharmaceutical companies simply cannot rely on supply sources that use antiquated methods of shipment. For example, it is unacceptable for chemicals or excipients to expire before the manufacturing process takes place, because their shipment was delayed or they were not shipped with proper temperature and humidity control. Additionally, every state has its own license requirements and

Continued on page 74.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2009, Vol. 29 No. 5

Filling instinct.

The time has come to take control. IMA Life introduces the latest technological breakthrough in sterile filling: XTREMA F2000. High performances, superb flexibility and easy implementation allow you to bring your sterile processing environment in line with your production objectives, adapting to your needs as they evolve.
Industry experience, proven technology, IMA Life expertise: ingredients which make the XTREMA F2000 much more than a machine.

www. ima.it/xtrema

PACK EXPO

Las Vegas, NV, USA - October 5-7, 2009
Visit us at Booth # C1819

IMA LIFE S.r.l. • *mktg.filling@ima.it* • *www.ima.it*
IMA NORTH AMERICA, INC. • *sales@imausa.net* • *www.imanorthamerica.com*

IMA LIFE
Aseptic Processing & Filling Solutions

VIAL LOADING • WASHING • DEPYROGENATING • FILLING • FREEZE-DRYING • STOPPERING • CAPPING

timetables for what can come in or out of the pharmaceutical production plant, and when this must happen. License requirements and special storage needs present one of the greatest challenges for both suppliers and third-party logistics partners assigned to build and implement supply chains strong enough to withstand the hardest knocks and unexpected events.

It is estimated that 80 percent of the active ingredients for drugs sold in the US originate in the global sourcing chain outside the country – a fact that received considerable publicity following a number of deaths linked to contaminated batches of the blood thinner heparin originally sourced in China. As a result, there has been growing pressure to disclose much more sourcing information than the existing FDA rules requiring drug companies to disclose the name and location of the manufacturer, packer, or distributor of prescription medications. New labeling standards could include sourcing disclosure for biological agents and bulking agents, each of which has its own supply chain around the globe. The only way this information can be identified and tracked is as the product of an efficient, properly constructed global supply chain.

Intermodal Shipping Concerns

Given the global sourcing of most drug manufacturers, an inefficient supply chain can create unnecessary storage and demurrage charges at ship terminals and airports, caused by information snags, missing or ill prepared shipping documents, and inappropriate cargo routing. The resulting cost penalties can dramatically add to the price of pharmaceutical products by creating huge and unexpected hidden costs. Poor quality of materials and inadequate packaging can lead to wholesale product destruction and poor or incomplete documents can result in delayed shipments. Such messiness when it comes to vendor responsibilities can lead to goods being rejected out of hand during border crossings, customs delays, cargo loss, and outright theft – all of which cost money. Switching cargo to airfreight or expedited airfreight services as a last ditch effort to solve the problem of incompetence and poor preparation may avert total disaster, but at a steep price.

Not understanding the marketplace also can have dramatic repercussions at every stage of building the supply chain. Those pharmaceutical manufacturers purchasing from overseas suppliers must coordinate closely with those responsible for shipping the goods to ensure they are intimately familiar with the customs rules and regulations of every country through which freight will pass, in addition to understanding the associated service parameters and costs. A lack of understanding about the freight marketplace can prohibit the import of vendor shipments or – more likely – add unanticipated customs costs, and possible exam fees. Additionally, a company can incur unanticipated freight costs or surcharges as a result of improper or inefficient routing of cargo.

The Freight Forwarding Relationship

In such a fluid transportation environment, pharmaceutical producers face a critical choice whether to use a local logistics provider or an international one. A local company will be cheaper and may have at least regional network coverage. But it can fall short in IT systems, standardized operations, and relationships with key international shippers. That makes a freight forwarding intermediary a virtual necessity. The best freight forwarders are at the vanguard of new technological advances and cutting-edge supply chain methodology. Their services can be customized for use by both the smallest and largest businesses and corporations. Freight forwarders can often find creative solutions where traditional supply chain handlers see obstacles. When it comes to challenges such as refrigeration, throughput, theft, customs, and other regulations, and product tracking, freight forwarders consistently solve problems in a non-traditional way that adds value.

For example, take the information technology that out of necessity plays a central role in today's evolving pharmaceutical logistics infrastructure, reflecting the emphasis on trace-back systems. An effective freight forwarder will have a computerized tracking system that offers a common language for businesses along the supply chain to capture essential product information and history. It is essential that computerized trace back systems provide an integrated information exchange platform that can be used across the supply chain, enabling information to be retrieved at any stage once a product has been shipped to the drug processor. The ideal program will show what has been shipped, what is in transit, what is due to be shipped, where goods are in the cycle, and how shipment is performing against the manufacturer's timetable. Via links to the freight shipper's own information, customers should be able to cross-check and validate progress and timings of shipments. Such a system will be flexible, and take into account the highly varied documentation and quality standard requirements of multiple national drug safety agencies, enabling one central system to be adapted to many export markets.

A professional logistics company represents the interests of full range of cargo and supply chain nodes. In addition to having a vested interest in the ups and downs of an entire region, freight forwarders have another ace in the hole: the government agencies responsible for customs clearance and other regulatory issues are much more sympathetic to the goals and aims of such a broadly-backed organization. Foreign supply chain networks should not be constructed without relying on seasoned guides who know how to improve throughput, navigate problems, and deal with the governments and ports.

In foreign countries where sourcing cannot be assured of the due process of law, such as China, it is vital to collect data and keep track of all freight in a way that creates a provable and thorough paper trail. Crime, loss, bureaucracy, and corruption must all be taken into account. Electronic tracking from a reliable freight forwarder is often the only way to overcome such roadblocks. Developing personal relationships are essential to understanding foreign business culture, and to cementing agreements between partners who may or may not speak the same language. By taking advantage of established freight-forwarding agents in the region, a pharmaceutical

producer can increase its ability to get results and track its goods effectively.

Hidden Shipping Costs

Working with a trusted freight forwarder also can be instrumental in helping pharmaceutical producers avoid the hidden shipping costs often implicit in the standard **In**ternational **Co**mmercial **Terms** (Incoterms). Incoterms were developed by the International Chamber of Commerce in the 1930s, and have been regularly revised to reflect transportation and documentation changes. They specify the exporting sellers and importing buyer's obligations regarding carriage, risks, and costs, and establish basic terms of transport and delivery. Incoterms only define contractual rights for delivery, and both parties must specify delivery terms and issues such as loss insurance and title transfer. In contrast to newer and smaller importers that generally specify Group C Incoterms (seller arranges and pays for shipping without assuming its risk), sophisticated importers prefer to use Group F terms, such as Free On Board (FOB). Increased supply chain visibility and the control of import shipments are critical FOB benefits. By taking control as cargo crosses the ship's rail at the port of origin, importers get better shipment management from their third party logistics provider.

Importers who are unfamiliar with the implications of Group C Incoterms, such as Cost, Insurance, and Freight (CIF), which designate that the seller pays all charges, may think they are more convenient, because everything is included in the final price. However, this also makes verification of the charges for freight and insurance difficult, meaning that importers generally wind up paying a higher price when the seller chooses the freight company. There are several reasons for this:

- The shipper does not have the vested interest or the leverage to get the best freight price.
- The shipper pays for the insurance, which could include substantial surcharges.
- Currency rates fluctuate widely, and the shipper may charge additional cost to cover them.
- Import quotas, bad weather, and other problems may add additional unexpected cost, which the shipper will cover using a higher rate.
- The shipper will charge a higher rate to cover its administrative costs.
- These and other related factors mean that shippers may build substantial additional freight charges into its rates, which often are not itemized for the importer.

These points all strongly suggest that sophisticated importers prefer to use Group F terms, such as Free On Board (FOB), giving them greater control over their shipments. Increased supply chain visibility and the control of import shipments are critical FOB benefits. By taking control as cargo crosses the ship's rail at the port of origin, importing manufacturers are better able to obtain accurate and timely shipment information through working with the third party logistics provider of their choosing. Because risk and cost transfer from the seller to the buyer in any case, as with CIF, pharmaceutical importers this way are able to manage and control their freight destiny.

The Impact of the CBP

Customs duties represent another source of hidden freight costs that negatively impact unwary companies in their global sourcing. The hidden shipping costs that we've just discussed are one area of concern. Another is the increased costs that will be imposed by new security regulations that will be enforced by the US Customs and Border Protection (CBP) Agency.

The SAFE Ports Act of 2006 directed CBP to gather data about shipments imported to the US that will allow the Agency to better evaluate terrorism and security risks. CBP is now in the process of finalizing rules for an Importer Security Filing (ISF) that requires importers to submit additional security-related information on their shipments at least 24 hours before the goods are loaded on board an ocean vessel. This ISF is in addition to the current 24-hour rule requirement to provide CBP with shipping manifest data in advance of cargo arrival.

It is clear that the ISF will fundamentally alter both the timeline and manner in which import related information is provided to CBP. As plans currently stand, the required filing must be made electronically and include 10 categories

Concludes on page 76.

of detailed identification regarding the manufacturer, shipper, consolidator, and importer, as well as information on the shipping container stuffing location and various shipment identification numbers. This information must be provided as individual line items so that shipments which contain merchandise subject to multiple classifications will require multiple ISF submissions. In addition, the carrier must provide CBP with two other items: a cargo stowage plan for the vessel, and container status messages. Thus, the ISF requirement is being referred to as the "10+2" rule.

The Import Security Filing will dramatically alter the supply chain information requirements. It is anticipated that the party who makes the ISF is responsible for the timeliness and correctness of the transmission, and must make every effort to verify the correctness of the data and to update the filing if there is any change in the data while the merchandise is in transit to the United States. Although some of the required data elements can be obtained from existing purchase order systems, most companies will be required to coordinate information from several different sources to satisfy the ISF requirements. It is not certain when the ISF requirements will be final, but it is clear that they will require importers to make major changes in how they gather and report information about their shipments. Such considerations will make partnership with a technologically sophisticated freight forwarding specialist even more necessary.

Security Impact on Air Cargo

The Importer Security Filing involves ocean shipping, but this is not the only link in the supply chain where security concerns will soon add greater complexity. In August 2007, President Bush approved the Implementing Recommendations of the 9/11 Commission Act of 2007. This legislation mandates 100 percent security screening of all cargo transported on passenger aircraft – a method of shipping that is often crucial for pharmaceutical producers and many other companies needing rapid or last minute shipments. It's estimated that this involves some 15 million pounds of freight daily, all of which must now be subject to a level of security screening commensurate to that of passenger baggage. The Transportation Security Administration (TSA) is responsible for the screening, which also will apply to cargo-only aircraft.

By August 2010, 100 percent of air cargo must be screened by TSA-approved methods prior to being loaded on a passenger aircraft with a preliminary requirement of 50 percent screening by February 2009. Screening must be done by breaking down pallet-wrapped shipments (PAX) into individual items with the number of pieces determined by shipper-level documentation. Screening can be by physical examination, x-ray examination, or using electronic explosives detection methods. Screening capacity at a single point in the supply chain is not sufficient to accomplish this requirement – and significant carrier delays, cargo backlogs, and transit time increases are expected.

TSA is pursuing a Certified Cargo Screening Program (CCSP) to allow screening of cargo early in the air cargo supply chain by a trusted, vetted, and audited facility. A facility approved for CCSP status must establish the integrity of a shipment through enhanced physical and personnel security standards, and verify the integrity of a shipment throughout the supply chain by utilizing stringent chain of custody methods. CCSPs can be located at shipping facilities, third-party logistics providers, warehouses and distribution centers, freight forwarding facilities, or manufacturing facilities. Certification is currently under way, and even pharmaceutical processors that do not frequently use air cargo would be well advised to establish a CCSP relationship.

It is certain that the new regulations will have an impact on cold chain logistics management for vaccines and other biologics shipped by air. Cold chains must operate by a quality management system in which maintenance of required temperatures is documented and verified through appropriate thermal testing. In today's methodology, certified test labs use environmental chambers to simulate ambient profiles that a package may encounter in the distribution cycle. Thermocouple probes measure temperatures within the product load to assure that temperatures do not reach outside of the required temperature range. However, the screening required under the new regulations could disrupt the necessary temperature assurance unless performed and documented under controlled conditions – another argument for partnering with a top quality CCSP freight forwarder.

Flexibility and Foresight

This discussion certainly doesn't encompass all the key considerations that pharmaceutical companies should consider in building their supply chains, but it does indicate that flexibility and foresight are essential to keep logistics problems from occurring in today's rapidly changing logistics landscape. Problems are inevitable for the unprepared or unsophisticated company that hasn't made supply chain design a priority. A well constructed supply chain doesn't just happen. It requires planning and analysis that encompasses all customer interactions from order entry through paid invoice, all product transactions, all regulatory requirements, and all market interactions for the final fulfillment of each order.

About the Author

Simon Kaye is Founder and CEO of Jaguar Freight Services with offices in London, New York, Philadelphia, Paris, Brussels, and Hong Kong, and an operations network in Europe, North America, South America, Australasia, Asia, Middle East, and Africa. Jaguar Freight Services provides a fully integrated door-to-door freight solution, including customs clearance, storage, and distribution facilities, and proprietary **Cybertrax**, real time online information tracking system. He can be contacted by telephone: +1-516-239-1900 or by email: simon@jaguarfreight.com.

Jaguar Freight Services, Ltd., 10 Fifth St., Suite 303, Valley Stream, New York 11581, USA.

In safe hands

Containment Solutions for the Pharmaceutical & Biotech Industries

- Barrier Isolation Systems
- Downflow Containment Booths
- High Containment Screens
- Pack Off and Process Equipment
- Kilo Labs & Glassware Enclosures

howorth
air technology

For further information please contact us on
North America 502 968 2065
Rest of the World +44 (0) 1204 571131
info@howorthgroup.com www.howorthgroup.com

ISPE's President reflects on the past 25 years of the Society's incredible history and discusses the challenge to become truly global; the importance of becoming a trusted technical resource for Members and regulators; and positioning the Society for success in the future.

PHARMACEUTICAL ENGINEERING Interviews

President and CEO, International Society for Pharmaceutical Engineering, Bob Best

Q Tell us about your educational background.

A I have two degrees in communications/marketing from the University of Notre Dame. I earned my undergraduate degree in 1972 and was able to complete my master's in 1975, while I was working for the University.

Q How did you begin your career?

A I started as a journalist with the Cincinnati Post and Times Star. I moved from there into public relations with Major League Baseball's Pittsburgh Pirates. I then went back to Notre Dame in a sports communications position before becoming the Director of Public Relations and Marketing for the Tampa Bay Buccaneers of the National Football League.

Q What prompted you to make a career change from what appears to be a very exciting job?

A I decided to make a change after 14 years in the sports world. There is no doubt that the sports industry is exciting. I enjoyed my years in it and consider myself fortunate for having had that opportunity. However, if you are not an athlete or a relative of team ownership, the chances for advancement are limited. At the age of 34, I felt it was time for me to move into the "real world" and find something with growth potential. I am not sure the "association world" fully qualifies, but it is a lot more real than the sports/entertainment industry and the Members we serve are performing a very real, critical function. In addition, my family and I also enjoyed living in the Tampa area so I looked for a position that would utilize my skills and experience and keep us in the area. ISPE was looking for an Executive Director and at that time, it appeared they were mostly in need of a marketing and operations person. I felt like it could be a good fit. ISPE was beginning its fifth year with lots of potential, but also lots of debt and doubt about its prospects for survival. I was looking for a new challenge and ISPE offered a significant one. I thought it would be something I would do for two or three years and then move on. Twenty-five years later, here I am!

Q How did you find out about ISPE?

A A friend of mine who knew I was looking for a career change had seen the job advertised and told me about it. I applied in October, was interviewed in early November during the ISPE Annual Meeting, which happened to be held in the Tampa area that year, was hired a week later, and began 2 January 1985.

Q What has been the single most exciting success in your 25 years?

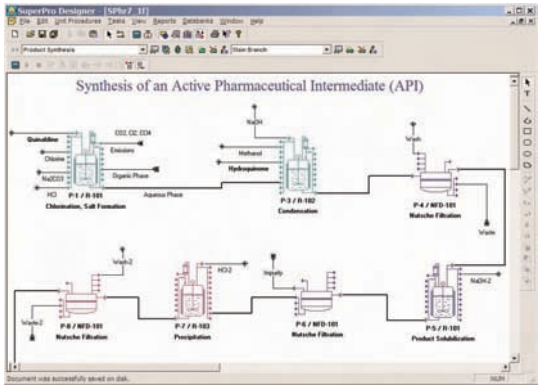
Continued on page 80.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2009, Vol. 29 No. 5

Intelligen Suite

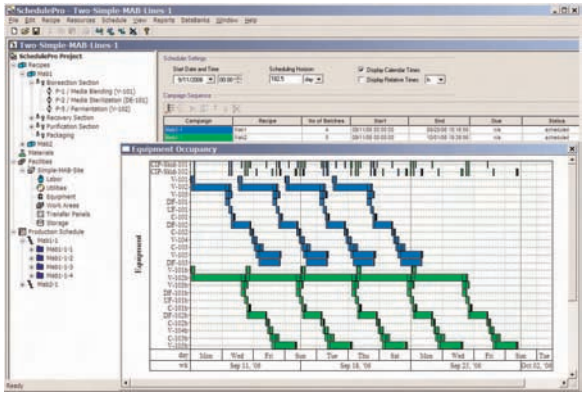
The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Single & Multi-Product Facilities

SuperPro



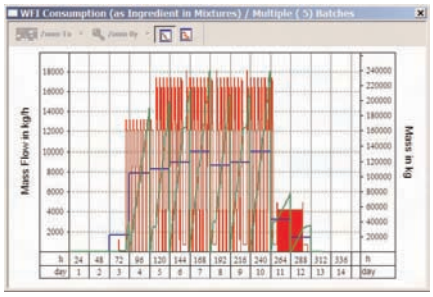
Use SuperPro Designer to model, evaluate, and debottleneck batch and continuous processes

SchedulePro

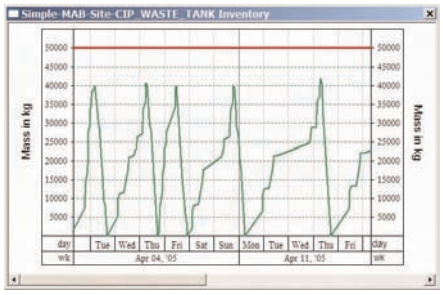


Switch to SchedulePro to schedule, model, and debottleneck multi-product facilities

Tracking of equipment occupancy in multi-product facilities



Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Inventory tracking for raw materials, intermediates, products, and wastes

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of biochemical, specialty chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 400 companies and 500 universities around the world (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile finite capacity scheduling tool that generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of facilities, equipment, resources and work areas. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size utilities for batch plants, identify equipment requirements, reduce cycle times, and debottleneck facilities.

Visit our website to download detailed product literature and functional evaluation versions of our tools

INTELLIGEN, INC. • 2326 Morse Avenue • Scotch Plains, NJ 07076 • USA
Tel: (908) 654-0088 • Fax: (908) 654-3866
Email: info@intelligen.com • Website: www.intelligen.com
Intelligen also has offices in Europe and representatives in countries around the world

"I think the biggest change is happening right now. Our industry is going through a major transition, both in its business model and technologically. Our strategic plan written three years ago forecast this and thrust us into a role as innovator, a catalyst for change."

A Wow! That is a tough one. In this business, everything is a team victory and I don't think we have sufficiently celebrated several impressive successes in ISPE's 29 years of existence. The Society started as essentially a USA educational organization. But in a relatively short amount of time, we have become truly global, no small feat for a not-for-profit organization. And both the industry and its regulators have come to rely on ISPE for the technical solutions we have been able to develop, thanks to some incredible dedication by hundreds of ISPE Members. So I believe our greatest accomplishments are becoming global faster than anyone could have projected and to have evolved beyond education into a role of creating valued standards for the industry.

Let me add that I do not believe that people fully comprehend how remarkable our growth has been, geographically and in program scope. Individual membership not-for-profit organizations like ours are constantly revenue challenged. The fact that we have Affiliates in 32 countries and Chapters throughout the USA, that we offer the range of services beyond the original intent and are only 29 years old is absolutely amazing. Sometimes we need to step back and reflect upon that.

Q How are we following up/expanding on these successes?

A Well, we have Affiliates and Chapters in nearly every key pharmaceutical region in the world. Yes, there are some countries left, but I believe we are very well positioned in that regard. I think we are capable of taking on even more responsibilities for the industry and the regulators, perhaps serving more extensively as a technical option to the major industry trade associations and to ICH.

Q What has been the most impactful change in the industry over the past 25 years? How did ISPE respond?

A I think the biggest change is happening right now. Our industry is going through a major transition, both in its business model and technologically. Our strategic plan written three years ago forecast this and thrust us into a role as innovator, a catalyst for change. Our Product Quality Lifecycle Implementation (PQLI) initiative is an example of how we can fulfill that role.

ISPE has gained respect, worldwide, and we are seen as a neutral body. That enables us to be an effective integrator. We have been successful in that regard by integrating industry and regulators on a scientific/technological level. We have done the same between operating companies and suppliers of service and equipment, taking the position that visionaries from all of those entities are part of the ultimate solution. We might also be able to serve as an integrator among traditional pharmaceutical, generic, and contract manufacturing companies, where I believe there is a need for someone to play such a role.

Q Looking back, is there a specific decision/direction that you would have done differently?

A I do not know any organization, armed with 20/20 hindsight, that cannot identify a whole host of things they would have done differently. In our case, I would say that most such cases would be related to saying "yes" to nearly every new initiative that comes our way. Ironically, that has also been a key to our success, but at the same time, it has also created resource issues which have been troublesome at times.

Q What has been the most significant impact that ISPE has had on the industry?

A I would have to say our technical documents. The Baseline® Guides and GAMP® 5 have become industry standards. The Baseline® Guides are the result of ISPE's integrator capabilities. Back in the 1990s, industry leaders believed that there were some dramatic misconceptions about FDA expectations on GMPs. They asked ISPE to arrange a dialogue with the FDA to either verify or refute these matters. The end result was an agreement for ISPE to provide the technical input, for FDA to review and comment, and for ISPE to deliver a document that reflected these conclusions that both industry and FDA could rely on for clarification. The Baseline® Guides have become a tremendously valuable tool for our industry. The GAMP® series has been similarly impactful.

Q Why did the FDA choose ISPE as the hub of the wheel that makes our industry turn?

A I am not sure we are the "hub of the wheel," but that is a nice sentiment. I do believe we have become a trusted technical resource in the eyes of the leaders of the FDA and that a similar perspective is spreading among regulatory authorities in Europe and Asia Pacific.

We are a non-lobbying group designed to serve all constituencies with neutrality, which means both industry and the regulators can rely on us because we have no agenda other than providing solutions. We are an individual membership organization not controlled by companies, but guided by the input of a diverse membership. We are truly global and few other organizations can claim that. We deliver. Our Members have taken on some important projects and in a relatively short period of time come through with tangible results.

I think the real break through for us was with the SUPAC Equipment Guide that we produced at the request of the FDA. They recognized that they had a need that they could not practically fulfill internally. They turned to us and we came through on a pace and at a level of performance that were truly remarkable.

Q What has been the secret to the success of ISPE over the past 25 years?

A **Collegiality.** ISPE is an organization that makes good things happen. Our Members and our staff are focused on helping others. I am amazed at the team attitude that pervades ISPE, especially having come from the sports world where egos are rampant. The attitude in this organization has been "If there is a need, let's find a way to deliver and not be concerned about who did what . . . just make it happen, just fix it." That is part of our culture, as is making sure that people feel welcome the very first time they show up at an ISPE activity. Our Members have always been willing to share, to help another Member find a solution to a problem. I have witnessed that in places where I was told that sharing was not a cultural norm. Well it is in the DNA of ISPE.

Commitment. When I started at ISPE the Society was $400,000 in debt. All the Members of the Board of Directors at that time had just signed for a loan, personally guaranteeing it. Can you imagine a stronger degree of commitment? Fortunately that sort of thing has not been required in recent years, but the dedication of our leaders, from directors on the International Board, to leaders of our many Affiliates and Chapters and the hundreds of committee, COP, and writing task teams, Members remains a strength of this organization. And let me add that such dedication has always been matched by our staff and advisors. The people who have worked for ISPE over the years could have been more highly compensated at other places of business. But they have chosen to be at ISPE because they recognize it as a special place. The chemistry between the volunteers and staff has been infectious.

Q How is ISPE recruiting and engaging regulators at the international level, other than FDA, EMEA, etc.?

A Among our many blessings has been to have some incredibly talented, well liked, and well connected former regulators involved as Members of our Regulatory Affairs Committee (RAC) and as our Regulatory Affairs Advisors. This started with Joe Phillips, who passed away suddenly last year, but who had made an incredible impact for ISPE over time. Joe had been employed by the FDA for 44 years and had been active on their behalf internationally. When he joined ISPE as an advisor he solidified and expanded our relationships here in the USA, but also in Europe and Japan.

Continued on page 82.

In Asia Pacific, Bob Tribe is our Regulatory Affairs Advisor. Bob not only held a senior position with Australia's TGA for more than 30 years, but he if a former Chairman of PIC/S. Upon his retirement from TGA, he became a consultant for PIC/S, WHO, and ISPE. And in Europe, John Berridge is our Regulatory Affairs Advisor. John is not a former regulator, but rather a senior manager from industry. However, he had been actively involved in ICH activities as a representative from EFPIA and in that capacity developed an excellent network within Europe and also among the other ICH regulators.

These gentlemen, former regulators Chuck Hoiberg and Paul D'Eramo, and current ICH participants Bob Baum and Georges France, all of whom are members of the RAC, have opened many doors for ISPE. In addition, I spend a great deal of my time expanding relationships on the regulatory front, especially in Asia.

Q Where do you see the Society five to 10 years in the future?

A Had you asked me that question a year ago I could have given you an answer with some confidence, though I would have probably been proven wrong. I do a lot of reading and listening and I must say the future is a bit cloudy. Certainly the current economic recession, which has had such a dramatic impact on all industries, will eventually swing in the opposite direction, as it always does, and that will have a positive affect. However, it is the current transition of our industry that is a little less clear. As I am doing this interview our leadership is preparing to meet to make just such a projection. We have done our homework and I am confident we will settle on a vision of where the industry is headed that will turn out to be accurate.

One thing is certain. Our industry will be much different 10 years from now than it is today. That might sound obvious, but frankly for my first 25 years with ISPE our industry has changed very little. I am pleased to say that the ISPE leadership has been very good at strategic planning, so I am confident our planning sessions will result in a clear direction for ISPE, one that will position the organization for success as the industry evolves.

Q Why is ISPE based in Tampa, FL?

A The two men who originally conceived of ISPE, Don Cattaneo and Paul Simmons, lived in Tampa when ISPE began in 1980. They did most of the initial startup work and incorporated ISPE in the state of Florida. As you would expect, the organization started with no funding and back in the 1980s, Tampa was an inexpensive place to operate.

Right before I was hired, the Board of Directors actually considered the possibility of relocating the Society to New Jersey, the center of the industry in those days. However, when they did the math, they determined that the Society could not afford to make such a move so ISPE remained in Tampa.

Because of the way business is done these days it really does not matter where an organization like ours is located since so much of what we do is accomplished electronically.

Q Who do you view as our main competition and what sets ISPE apart?

A Within the not-for-profit arena, it is hard to think in terms of "competition" in the traditional business sense. ISPE was started because there was a niche . . . technical professionals . . . that the founders believed was not being well served. That remained true for about the first 15 years. Then several enterprising for-profit educational groups and publications recognized an opportunity and started to produce programs similar in content to ours. That trend continues today and they do represent a competitive threat to us.

There are other associations that overlap to an extent, both in programming and membership base. Whenever possible, we try to work with them for the good of the industry. As a volunteer driven organization, we consider our leaders' time precious so we must be sensible, especially at this point in our history, to eliminate redundancy whenever possible. Companies are less able to sponsor their employees to work on the types of projects we are engaged in so we must do our best to ensure we are not overlapping in what we attempt with other organizations.

Q Where will ISPE's international growth be in the future?

A As I mentioned, I believe we are already well positioned thanks to the dedication of hundreds of leaders from our Affiliates around the world. However, based on the anticipated expansion of the industry into Asia, Eastern Europe, and Latin America, clearly our greatest opportunity for growth will come from those regions.

Q What have been the challenges in developing the international Affiliates?

A Frankly, after scaling the mountain of expansion into Europe in the early 1990s, it has been mostly downhill from there. The learning curve and growing pains in establishing the Society in Europe were immense. For ISPE, we were inventing a wheel. We had no experience in starting a business in Europe, few Europeans on hand to guide us at that time, and precious little funding. Expanding any business into a new continent is complex and expensive, even with a road map in place. We made up most things as we went along. Fortunately, in addition to our ignorance, we also had the belief that this was the right thing to do and the commitment to stick it out. More importantly, as has always been the case, we found people in all the Affiliate countries who became passionate about ISPE, so much so that they overlooked our operational short-comings and gave us the wisdom to enable us to succeed.

With all the errors that we made along the way, we did make one decision that was the most important of all. Unlike other American based groups that

expand overseas and attempt to impose US ways of doing things, we wanted the Affiliates to develop programs and approaches that were appropriate to their countries. Certainly, there were some processes that had to be consistent throughout the Society, for Affiliates and Chapters, but those were and continue to be relatively few. I believe our Affiliates and Chapters have been able to operate fairly independently and be innovative in their areas.

Interestingly, we have learned that as different as we believed Europe is from North America, Asia is even more complex from a business perspective. Fortunately, the experiences in Europe taught us to be flexible in our planning. Now that we have a critical mass of Members and Affiliates in Asia Pacific we have determined that it will be essential to regionalize our approach to best serve our Members and assist our volunteer leaders. We are changing our strategic and operational plans to accommodate this thinking.

Q Have you visited all the Affiliates?

A I have been to all but five and have had a hand in launching the majority of them. For me, that has been one of the most rewarding experiences in my life. Meeting people from all over the world, learning about their cultures, business customs, and legal systems, and then working with them to establish something worthwhile will be something I will remember and value for the rest of my life.

Q What do you do on a routine basis – what is a typical day like for you?

A I frequently reflect about the way the answer to that question has changed over the years. When I started in 1985, I was one of four full time employees. For probably the first 15 years here, I spent almost the entire day on the phone. I remember the staff joking about how they would race over to my office when they saw the light on my phone line go off so they could catch me between calls. Now, I spend almost my entire day, and lots of the night, sending and replying to emails.

Certainly, I have specific projects that I initiate, mostly strategic initiatives and business development tasks. But I consider myself an enabler, both for staff and our volunteers. I believe the most important thing I can do is to get information in the hands of those doing the work of the Society. I feel especially strong about that when it comes to the volunteers. If someone is trying to do good work and they need input from me in order to accomplish it, I need to get that to them as quickly as possible. So I am passionate about returning emails quickly. As a global organization, those emails come in 24 hours a day so I try to be responsive early in the morning before I come to the office, throughout the day, and at home at night.

Beyond that I spend a great deal of time with the staff, those in the

Concludes on page 84.

headquarters office and in our offices in Brussels, Singapore, and Shanghai. I have several direct reports, but also try to be available to other departments that might need my assistance.

Not surprisingly because of our global reach, I travel about one third of my time, much of it outside the USA.

Q How is ISPE responding to the current economic climate?

A We expected hard times were coming, but the enormity of the global recession made the impact far worse than anticipated. Fortunately, we had accumulated a cash reserve for just a situation. We started with a lean budget for 2009, but have made 17% in expense cuts from that. As with many other companies, regrettably, this has included a reduction in staff. We have been careful not to make reductions that would adversely impact our ability to deliver the tools and services our Members have come to expect from us.

Since volunteers are the ones responsible for the true gold nuggets ISPE provides . . . knowledge . . . we must also keep a close eye on their constraints. Many companies have imposed travel restrictions so we have had to quickly redesign many of our SOPs to accommodate that reality.

They say that you test the true metal of a person or organization during tough times. If that is true, I am now even more convinced of the viability and longevity of ISPE. Our volunteers and staff have absolutely risen to the occasion. I have witnessed our best thinking and strongest efforts this past year. We will come out on the other end as a more efficient organization and more closely targeted to the needs of our Members.

Q What are the major challenges running an organization of volunteers? How do you motivate the volunteers?

A I cannot take credit for that. ISPE has always had a long line of people passionate about the organization, visionary in the ways to improve it, and committed to the tasks necessary to succeed. We on the staff are here to make that as easy and effective as possible, but few are the times when we have to "nudge" the volunteers to action.

Q How have you been able to maintain such a loyal staff in Tampa?

A I guess you probably need to ask them. I am proud that we have had so many people stay with ISPE for a good part of their career, and make significant contributions along the way. I try to give the staff the ability to apply their own styles to their positions, establishing some goals for them, but then getting out of their way. I am genuinely concerned about every person who works for ISPE, in all of our offices, and will always do whatever I can to help them succeed, preferably with ISPE, but wherever they may decide to go.

Q What is the purpose of the International Leadership Forum (ILF)? How has it positively impacted ISPE?

A The ILF is actually the 21st century version of what was known as the Pharmaceutical Advisory Council (PAC). The PAC started in the early 1990s and was made up of Vice Presidents of Engineering from the multinational companies based in the USA. It was this group that motivated the development of the Baseline® Guides, as I discussed earlier. As ISPE expanded, both beyond its initial focus on "engineering" and also geographically, the leaders of the PAC believed that body needed to be reconfigured. So now the membership constituency includes Presidents or Senior Vice Presidents with global responsibility, in the areas of quality, engineering, manufacturing, and development, from pharmaceutical, biotech, generic, and contract manufacturing companies, from all over the world. They have been incredibly helpful to the Society, in particular to our strategic planning, but also in providing resources, mostly in terms of contributors to our Body of Knowledge. As the years have gone by, they have become even more hands on. They were the motivators of Product Quality Lifecycle Implementation (PQLI) initiative and have recently begun work on an important Supply Chain Security project.

Q What will be your legacy to ISPE?

A If you are looking for specific metrics I suppose it would be development of a truly global organization and a sound business foundation. When I started, we had 500 Members, were badly in debt, and aside from a handful of international Members were completely USA centric. Today, we have 24,000 Members in 90 countries and despite the impact of the global recession have significant reserves. Certainly, I am proud of that, and do believe I have made a contribution toward it. But my primary contribution has been as a facilitator, spotting a whole lot of talented people, getting them into the right slots, and letting them make things happen for the truly vibrant organization that ISPE has become.

Q What interests you/keeps you busy in your personal life?

A So you saved the most sensitive question for last. ISPE has been a very important part of my life for a quarter of a century. I would like to think my family has always ranked first, but the demands of running an international organization as complex as ours often take me away from them. So when I am home I try to do the things they want. They are my interest. Early next year those interests will expand. My daughter is expecting a child in January so my wife and I officially jump into a new generation in our family. I relish the thought of becoming a grandfather.

On a rare occasion, I manage to sneak out on the golf course. I am a current events fanatic and read as much as I can and watch news outlets that I consider reliable and worthwhile. And as you might expect from my previous "life," I remain a sports fan.

Latin America

Brazil

New Certified Reference Substance[1]

Resolution RDC 32 has established a new reference substance, ceftriaxone sodium, according to studies of certification coordinated by the Comissão Permanente de Revisão de Farmacopéia Brasileira (CPRFB). The use of this reference substance is mandatory for the manufacture and quality control of raw materials and medicinal products that must be compared to a reference substance. This resolution became effective on 9 June 2009.

Mexico

GMP[2]

The Mexican Norm NOM-059-SSA1-1993 provides information on Good Manufacturing Practice for establishments of the pharmaco-chemical industry involved in the production of medicines. It includes definitions of relevant terms, the requirement for the design and organization of an establishment in the chemical/pharmaceutical sector, manufacturing control, manufacturing equipment, technical and legal documentation, destruction of waste and residues, and the classification of different areas. The modifications to this norm include explanation of which institutions/organizations took part in the development of this Norm; deviations or non compliance; devolutions and complaints; recalls, validation, change control, and technical audits. These chapters follow the US Code of Federal Regulations, Parts 210 and 211.

This Norm replaces Official Mexican Norm NOM-059-SSA1-1993 and became effective on 19 June 2009.

Europe

Austria

Decree on Trade and Consumption of Narcotics[3]

The Decree on Trade and Consumption of Narcotics (374/1997) provides information on the production, manufacturing, transformation, purchase, possession, and delivery of narcotics and their corresponding authorization. It also details the required documentation for producers, wholesalers, manufacturers, doctors, dentists, and pharmacists; as well as the requirements for packaging; prescription and delivery; maximum quantities allowed. For medicinal products containing narcotics, it details the first aid and substitution therapy; export and import licenses; facilities of the United Nations located in Vienna and transitional provisions. This Decree on Trade and Consumption of Narcotics has been amended to include new substances.

Ireland

Quality Defect Investigation Reports[4]

The Irish Medicine Board (IMB) have released a guide to address the format and content required for quality defect investigation reports for medicinal products.

The following categories are included in the guide: medicinal products which are the subject of a Marketing Authorization (MA) or registration; medicinal products manufactured in Ireland which are distributed in Ireland or elsewhere; medicinal products distributed inside and outside the EU by Irish wholesalers and exporters; promotional samples of medicinal products issued to healthcare professionals; exempt medicinal products for human use which are supplied to the order of a registered doctor or a registered dentist for use by his/her individual patients under his/her direct personal responsibility, or in the case of unauthorized veterinary medicinal products, medicinal products supplied in accordance with the cascade system; investigational medicinal products manufactured and distributed for the purposes of performing clinical trials.

Turkey

Required Documentation and Conditions for Opening Manufacturing Sites[5]

This document published by the IEGM General Directorate of Pharmaceuticals and Pharmacy, provides the list of documents and conditions required for the opening of manufacturing sites of medicinal products, active ingredients of medicinal products and intermediate products, according to the provisions of the By-Law on the Manufacturing of Pharmaceutical Products.

The required documentation are from the General Director of the manufacturing site; responsible person(s) of manufacturing; responsible person(s) of quality control; responsible person or team of quality assurance; manufacturing site; SOPs regulating the activities of the manufacturing site; particularities of the water and aeration system together with a plan; original or notary-approved document of the authorization of non-hygienic establishment; report on the evaluation of the environmental impact and proof of fee payment.

EMEA Updates

DG ENTR Conclusions on Study on Pharmaceutical Excipients[6]

Following the publication of a report on an impact assessment study at the beginning of June 2009 by an external contractor, DG Enterprise and Industry has taken the decision not to continue with the preparation of a Commission Directive on GMP for certain excipients as originally foreseen in Article 46(f) of Directive 2001/83/EC.

Reference Medicinal Product[7]

On the 18 June 2009, the European Court of Justice ruled that Directive 2001/83/EC is to be interpreted as meaning that a medicinal product which falls outside the scope of Regulation No. 726/2004, and the placing of which on the market in a Member State was not authorized in accordance with the applicable Community law, cannot be considered to be a reference medicinal product within the meaning of Article 10(2) (a) of Directive 2001/83.

The Court stated that to allow a medicinal product benefiting from an authorization issued on the basis of national provisions alone to be considered to be a reference medicinal product would amount, in fact, to authorizing an exception to the rule, laid down in particular in Article 6(1) of Directive 2001/83 that a medicinal product which has not been authorized in accordance with Community law may not be placed on the market of a Member State.

Transgenic Animals in the Manufacture of Biological Medicinal Products[8]

On 25 June 2009 the EMEA released a concept paper to propose a revision of the Guideline on the Use of Transgenic Animals in the Manufacture of Biological Medicinal Products for Human Use.

The current guideline became effective in July 1995 and the production method for recombinant proteins is transgenic animals has progressed significantly. This revision aims to adapt aspects of the quality guidance already in place for other production systems to the special case of transgenic animal systems.

Variations (codecision part): Publication of Amendments to Directive 2001/82/EC and Directive 2001/83/EC[9]

A new Directive 2009/53/EC has been published in the Official Journal on 30 June 2009 regarding variations to the terms of marketing authorizations for medicinal products. This Directive is part of a global revision of the legal framework on variations to make the overall system clearer, simpler, and more flexible, and it amends the legal basis for the adoption of Community rules on variations in order to harmonize those rules for all authorized medicines in the EU.

Asia

China

Verification and Inspection of Accreditation of Clinical Trials[10]

This notification is issued to stipulate the goals, timeline requirements, procedures, and criteria for verifying, inspecting, and re-granting the accreditation for clinical trial sites qualified by governments.

All clinical trial sites must be qualified by China State Food and Drug Administration (SFDA) and the Ministry of Health (MoH). When this is not the case, the site cannot participate in any Phase I to Phase III studies for any therapeutic fields. The accreditation is valid for three years and before the accreditation validity, China SFDA needs to re-verify and inspect each accredited site and see if they are up to the standards.

There are currently 325 clinical trial sites (hospitals) qualified for drug clinical trials in China.

International

WHO

Procedure for Assessing the Acceptability, in Principle, of Active Pharmaceutical Ingredients for use in Pharmaceutical Products[11]

The World Health Organization (WHO) released the Annex 4: Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products.

This quality assessment procedure is to evaluate whether APIs meet the requirements recommended by the WHO, and that they are manufactured in compliance with WHO good manufacturing practices. This will be done through standardized quality assessment and inspection procedures.

Continued on page 46.

Australia

Therapeutic Goods Charges Regulations 1990: Fees[12]

The Therapeutic Goods Agency (TGA) amended The Therapeutic Goods (Charges) Regulations, which prescribes the annual fee for the registration and listing of therapeutic goods and licensing of manufacturers of therapeutic goods as imposed by the Therapeutic Goods (Charges) Act. This became effective on 10 July 2009.

Canada

Proposed Amendment: Adverse Drug Reaction Reporting[13]

Amendments to Division 1 of the Food and Drug Regulations have been proposed in order to require manufacturers to notify the Minister of a significant safety signal arising from the annual summary report. The amendment also will clarify when the Minister can request case reports or summary reports and enable the Minister to request case reports or summary reports when they consider it necessary to establish the safety of a drug under the conditions of use recommended.

United States

cGMP[14]

A Questions and Answers document, Level 2 guidance, providing answers to questions and clarifying existing requirements and policy regarding current Good Manufacturing Practices (cGMPs) for human, animal, and biologics medicinal finished products has been published. This guidance has been updated with questions and answers relating to equipment, control of components and drug product containers and closures, production and process controls, laboratory controls, records and reports, and has been updated with a cGMPs penicillin drugs section.

Incorporation of Physical-Chemical Identifiers into Solid Oral Dosage Form Drug Products for Anti-counterfeiting[15]

On 14 July 2009, the Food and Drug Administration (FDA) released a draft guidance that details recommendations to pharmaceutical manufacturers on design considerations for incorporating Physical-Chemical Identifiers (PCIDs) into Solid Oral Dosage Forms (SODFs).

The guidance provides supporting documentation to be submitted in New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs), to address the proposed incorporation of PCIDs in SODFs,

It also includes supporting documentation to be submitted in post-approval submissions to report or request approval to incorporate PCIDs into SODFs, and procedures for reporting or requesting approval to incorporate PCIDs into SODFs as a post-approval change.

This draft guidance also provides FDA recommendations regarding evaluation of toxicological and other concerns for PCIDs that are incorporated into packaging and labeling and procedures for reporting or requesting approval to add PCIDs to packaging and containers as a post-approval change.

Abbreviated New Drug Applications ANDAs – Impurities in Drug Substances (Revision 1) (Final)[16]

This FDA released guidance details recommendations on Chemistry, Manufacturing, and Controls (CMC) information to be included in the report submitted on acceptance criteria for residual solvents in drug substances and products. This guidance is aimed in particular to products proposed in original Abbreviated New Drug Applications (ANDAs), Drug Master Files (DMFs), including type II DMFs, and related supplements.

Recommendations for establishing acceptance criteria for impurities in drug substances also are provided in this guidance as well as information regarding identification and qualification of impurities in drug substances.

This document replaces the Draft Guidance for Industry: ANDAs: Impurities in Drug Substances (Revision 1), Jan-2005.

Labelling Change for Leukotriene Modifiers[17]

On 12 June 2009, the FDA requested manufacturers to include warnings in the drug prescribing information for SINGULAIR (montelukast), ACCOLATE (zafirlukast), ZYFLO and ZYFLO CR (zileuton), asthma drugs known as leukotriene modifiers. This request follows neuropsychiatric events that have been reported to the FDA, such as anxiousness, mood changes, or suicidal behaviors.

Leukotrienes are substances in our bodies thought to cause allergy and asthma symptoms. Leukotriene modifiers work by blocking leukotrienes or by stopping the formation of certain substances that cause swelling, tightening, and mucus production in the airways.

Immunosuppressant Drugs: Labeling Changes[18]

On 14 July, the FDA published a document in order to require that manufacturers of RAPAMUNE (sirolimus), SANDIMMUNE (cyclosporine), NEORAL (cyclosporine modified), CELLCEPT (mycophenolate mofetil), and MYFORTIC (mycophenolic acid) to update labeling to include stronger warnings, about the risk of opportunistic infections, such as activation of latent viral infections, including BK virus-associated nephropathy. This FDA requirement is a result of analyses conducted by the FDA of its Adverse Event Reporting System (AERS) that emphasized the association between BK virus-associated nephropathy and the use of these immunosuppressant drugs. These drugs are used to protect against the rejection of certain organ transplants, and have been associated with BK virus-associated nephropathy, and other infections, which may lead to serious outcomes, such as renal allograft loss.

References

1. Diário Oficial da União (DOU), Legislation, Official Journal, No. 108 of 09-Jun-09 (Section 1, p.47), http://www.in.gov.br.
2. Diario Oficial de la Federación, (DOF): 22-Dec-2008.
3. Bundesgesetzblatt, Legislation, Official Journal, Teil II, Nr. 173/2009 vom 15. Juni 2009, http://www.digitalegesetze.at.
4. Agency, IMB, Medicines Agency, http://www.imb.ie.
5. Agency, IEGM, Medicines Agency, http://www.iegm.gov.tr.
6. EMEA update, 09 June 2009, http://www.emea.europa.eu/.
7. EMEA update, 18 June 2009, http://www.emea.europa.eu/.
8. EMEA update, 25 June 2009, http://www.emea.europa.eu/.
9. EMEA update, 30 June 2009, http://www.emea.europa.eu/.
10. SFDA, http://eng.sfda.gov.cn/eng/.
11. http://www.who.int.
12. Obtained from the Commonwealth of Australia Law (ComLaw) Web site, http://www.comlaw.gov.au.
13. Canada Gazette / Gazette du Canada, Legislation, Official Journal, I Volume 143, No 24, 13-Jun-09, http://www.canadagazette.gc.ca/PartI.
14. Agency, CBER, CBER, CDER, CDER, CVM, CVM, Center, FDA, Medicines Agency, ORA, http://www.fda.gov/cder.
15. Agency, CDER, CDER, Center, FDA, Medicines Agency, Volume 74, Number 133/Pages 34021 – 34022, Docket No. FDA-2009-D-0212, http://www.accessdata.fda.gov.
16. Agency, CDER, CDER, Center, FDA, Medicines Agency, http://www.fda.gov.
17. Agency, FDA, Medicines Agency, http://www.fda.gov.
18. Agency, FDA, Medicines Agency, http://www.fda.gov.

This information was provided by Frank Sayala, Pharmaceutical Research Associates (UK).

Annual Meeting to Focus on Thriving in a Survival Environment

The 2009 ISPE Annual meeting will be held 8-11 November in San Diego, California, USA. This year's theme is Thriving in a Survival Environment. The following are highlights of what to expect at the Keynote Session and in 11 topical tracks:

Keynote Session

This year's Annual Meeting Keynote Speakers are:

- **Samuel Bogoch MD, PhD,** is chairman of Replikins, Ltd., in Boston, Massachusetts, USA, and faculty at both Harvard Medical School and the Boston University School of Medicine. Dr. Bogoch's areas of research include chemical structure and virus receptor properties of brain gangliosides, inhibition of virus attachment to brain cells, structure and function of brain glycoproteins, biochemistry of cancer, serum antibodies to cancer antigens, the replikins, genomic peptides associated with rapid replication, quantitative relation of replikins to virus outbreaks, and advance warning of H5N1.
- **Antonio J. Ricco** is Chief Technologist for Small Payloads and Instrumentation in NASA Ames Research Center's Small Spacecraft Division, on loan from Stanford University's Department of Electrical Engineering and Center for Integrated Systems. At NASA, Ricco develops remote, autonomous bioanalytical systems for fundamental space biological studies; serves as chief technologist for the GeneSat, PharmaSat, and O/OREOS flight projects; and is instrument lead for the MEMS-based NIR spectrometer on the LCROSS lunar impactor. Ricco is Vice President of the Transducer Research Foundation and a member of NASA's Lunar Exploration Analysis Group.
- **Lembit Rägo MD, PhD** is Coordinator, Quality Assurance and Safety: Medicines Essential Medicines and Pharmaceutical Policies at the World Health Organization (WHO) in Geneva, Switzerland. In December 1999, he joined the WHO in the Department of Essential Drugs and Medicines Policy where the areas of medicine nomenclature, quality standards, regulatory guidelines, safety and pharmacovigilance, are addressed. Since 2000, he has been the WHO observer to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Steering Committee.

Education Sessions by Track

Many of this year's education tracks correspond to a Certified Pharmaceutical Industry Professional™ (CPIP™) Knowledge Element. CPIP is a competency-based international credential. Please visit the Annual Meeting section on the ISPE Web site for a listing of sessions in each track.

- **Survival**
  ISPE education sessions are created by ISPE Members who work every day in the same environment that you work and face similar challenges. As Volunteers, ISPE Member presenters bring their ideas to the Annual Meeting table sharing knowledge, insight, and application through these education sessions, aiming to strengthen the pharmaceutical environment through this medium.
- **Product Development**
  (CPIP Knowledge Element 1)
  CPIP Knowledge Element One includes: formulation, clinical phases, and manufacture; technology transfer; production scale-up and optimization.
- **Facilities and Equipment**
  (CPIP Knowledge Element 2)
  CPIP Knowledge Element Two includes: design and construction/installation; commissioning and qualification as a risk management strategy; operation and maintenance; controls and automation.
- **Information Systems**
  (CPIP Knowledge Element 3)
- **Supply Chain Management**
  (CPIP Knowledge Element 4)
  CPIP Knowledge Element Four includes: materials management; operational economics; warehouse and distribution management.
- **Production Systems**
  (CPIP Knowledge Element 5)
  CPIP Knowledge Element Five includes: production unit operations – drug (small molecule) and biologics; production management; production control.
- **Regulatory Compliance**
  (CPIP Knowledge Element 6)
  CPIP Knowledge Element Six includes: government regulations; standards, practices, and guides.
- **Quality Systems**
  (CPIP Knowledge Element 7)
  CPIP Knowledge Element Seven includes: risk management and Quality Management System (QMS); systems validation.
- **Investigational Products**
  The Investigational Products (IP) Community of Practice (COP) brings together industry professionals for interactive learning and networking opportunities. This year's sessions include educational topics that address challenges industry professionals face in their day-to-day lives, as well as emerging or strategic topics important for managers and decision-makers.
- **Project Management**
  The PM Community of Practice (COP) has chosen two distinct, large-scale projects to feature through six highly-interactive sessions for the Project Management Track.

Concludes on page 87.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

ILF Takes on Challenge of Global Supply Chain Integrity

The integrity of the pharmaceutical supply chain is becoming the focus of increasing concern and scrutiny. The supply chain is becoming more complex, the number of environmentally sensitive products is rising sharply, and the sophistication of counterfeiters is alarming. Consequently, the industry is facing increasing legislative scrutiny and guidance on ensuring the quality of its products throughout their entire lifecycle.

ISPE's International Leadership Forum (ILF) has established a Global Supply Chain Integrity workgroup to develop a guide that describes globally applicable practices to help secure the integrity of the pharmaceutical supply chain.

These practices include quality system and security practices that help prevent adulteration of products in the supply chain or the introduction of counterfeit products into the supply chain. The guide will also address practices that help prevent the diversion of products outside of legitimate channels of commerce. These illegitimate channels can result in the adulteration of products or the introduction of counterfeits into commerce. It will also cover the use of information to signal potential supply disruptions that could encourage the use of substandard or substitute materials by suppliers. The guide will also make recommendations on steps a firm should take when a signal of potential supply disruption is detected.

A second workgroup will develop an outline for a paper or document that describes technical standards for anti-counterfeiting measures and more detailed methods only covered in general in the guide.

ISPE's ILF provides an opportunity for thought leaders in the pharmaceutical industry to identify and influence direction and align the industry globally, establish dialogue with regulators to discuss critical technological issues, identify opportunities for innovation, promote consistency, and seek worldwide harmonization where appropriate. PE

Annual Meeting...

Continued from page 86.

- **Supplier-Focused**
  Suppliers offer a superb knowledge resource. This year, sessions of particular interest to suppliers are listed as a track to recognize this important facet of ISPE educational programming. PE

ISPE Launches Operations Management Community of Practice

ISPE has launched the Operations Management Community of Practice (COP). This new COP aims to cover and review all areas of operations management including the integrated process flow, from raw materials supply to final product distribution. The goal is to better understand how a complex pharmaceutical manufacturing plant can work more efficiently to increase productivity.

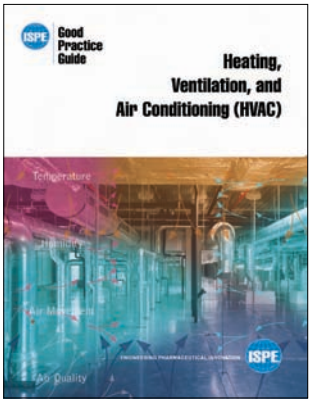
"In the past, pharmaceutical companies have always considered manufacturing as a matter of compliance with regulatory requirements (GMP)," said Operations Management COP Chairs Giuseppe Ravizzini and Alain Cruset. "Currently, due to decreasing rate of innovation, increasing costs for R&D and increasing variety of customer preferences, operations have started to implement tools and methodology to improve performance and efficiency."

"It is essential to learn from other industry sectors, to improve industry sectors, to improve technological and management aspects, from strategic issues to planning and shop floor execution."

The COP has identified 10 main areas of competence that the group will focus on in future discussions, meetings (on the Web or live), work teams and other initiatives. To read more about these areas, you can visit the Operations Management COP by following these instructions:

- Log in at www.ispe.org/cops
- Click on Join/Unjoin COP
- Scroll down to Operations Management COP and place a check mark in the box
- Click the "Join" button in the bottom right corner

HVAC Guide Helps Determine User Requirements and Functional Design



Heating, Ventilation, and Air Conditioning (HVAC) systems are employed for human comfort and to protect people and product. HVAC systems also can protect the outdoor environment from hazardous material removed from the work place via HVAC exhaust.

HVAC systems can be critical systems that affect the ability of a pharmaceutical facility to meet its objective of providing safe and effective product to the patient. Systems that are properly designed, built, commissioned, operated, and maintained can help ensure the quality of product manufactured in that facility, improve reliability, and reduce both first cost and ongoing operating costs of the facility.

In the pharmaceutical industry, HVAC design engineers need to deliver a GMP compliant design for a particular process application that meets key customer requirements and complies with local codes and standards. To successfully deliver such a design, the HVAC engineer also must understand how those systems integrate into and are affected by other aspects of the facility design and operation. The HVAC engineer must coordinate with other disciplines for a successful project.

The ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC), expected to be released in October, provides designers and the project team with suggestions to help determine the user requirements and the functional design that define the facility's objectives. It also provides options to be considered in creating a design that has low lifecycle cost and which is sustainable.

ISPE Singapore Conference 2009 a Success

With the theme of "Advancing Excellence and Innovation in Regional Pharmaceutical Manufacturing," the ISPE Singapore Conference 2009 was held 31 May – 2 June at the Suntec Convention Centre, Singapore. Eight facility visits were also organized for delegates on 3 June.

Attended by 216 registered delegates from the region participated in a program that included topics relating to sustainable solutions, regulatory, automation, manufacturing excellence, contract manufacturing, and validation.

Affiliate representatives of all nine Affiliates (Australasia, China, India, Indonesia, Japan, Korea, Singapore, Philippines, and Thailand) in Asia Pacific gathered in Singapore for the Asia Pacific Affiliate (APAC) meeting on 2 June, held alongside the ISPE Singapore Conference. Leaders discussed the possibility of collaborating on regional training programs and conducting potential webinars that would be of interest to industry professionals in Asia Pacific. The Affiliate leaders also explored various approaches of promoting to the region benefits of ISPE's Communities of Practice (COPs) and Certified Pharmaceutical Industry Professional™ (CPIP™) program.

The meeting concluded with dialogue with Jacques Morenas, Assistant Director of the Inspection and Companies department in the French Health Products Safety Agency (AFSSAPS) and chair of the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

Online Learning Conveniently Delivers Quality Education

These days, time is more valuable than ever and sending just one employee to attend an offsite education program is more than most work schedules and company budgets can handle.

Alternative, more convenient ways of educating employees need to be available to companies, and ISPE offers such options through its Online Learning Program. The same quality education found at an offsite event is delivered by computer with Internet access.

Industry and regulatory professionals working in the field develop and lead ISPE Online Learning events and courses, so learning comes straight from experts with current knowledge and cutting-edge perspectives. For a broad range of choices, ISPE divides its forms of Online Learning into these families:

Live Webinars – Real-time presentations by industry experts and regulatory professionals.

Recorded Webinars – Recorded versions of live webinars. Participants can take the time they need and enjoy important presentations at their convenience.

Webcasts – Video recordings of ISPE conference education sessions.

Podcasts – ISPE education and information briefs for hand-held devices.

Online Courses – On-demand learning for fundamental to advanced knowledge on relevant and timely subjects, and to help meet regulatory training requirements. Interactive learning experience includes a downloadable course presentation, learning reviews/assessments highlighting important points, hot-links to information, and an online resource handout as a quick reference.

Basic Industry Knowledge and Certified Pharmaceutical Industry Professional™ (CPIP™) Online Courses – Self-directed courses providing a range of learning opportunities for career growth and professional development. For those interested in general pharmaceutical industry knowledge on topics ranging from drug product development to manufacturing, and those seeking the CPIP™ (www.ISPE-PCC.org) credential.

GMP Online Courses – Education on different standards, laws, regulations and guidelines impacting GMP compliance and quality.

Product Quality Lifecycle Implementation® (PQLI®) Webinars – Sessions with subject matter or discussions tied to the PQLI initiative (www.ISPE/org/PQLI).

Aside from an employee being in the same room as a presenter, ISPE Live Webinars are no different from an offsite conference seminar or training course. Participants listen to discussions as they would in a classroom, and have the opportunity to directly question and answer speakers on the other end of the live event. Plus, novel, interactive features such as polling and voting during discussion are available.

At only $79 for ISPE Members ($179 nonmembers) for a Live Webinar, $49 for ISPE Members ($149 nonmembers) per Recorded Webinar, and $149 for ISPE Members ($199 nonmembers) for each Online Course, ISPE Online Learning is a viable alternative to education-related travel.

Training a group of employees at once is another convenience. ISPE welcomes webinar purchasers to share a live or recorded event with as many colleagues as possible. This can be done by gathering a group in a conference room or common area and broadcasting a webinar via laptop and projector.

Lists of upcoming live webinars, online registration, and a catalog of all ISPE recorded webinars are available at www.ISPE.org/onlinelearning.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

2008-2009 *Pharmaceutical Engineering* Article of the Year Finalists

We are pleased to announce the 2008-2009 Roger F. Sherwood Article of the Year Award Finalists. The winner will be selected from this group and recognized at ISPE's 2009 Annual Meeting.

September/October 2008, Volume 28, Issue 5
Functional Safety in the Life Science Industries
by David Hatch, Iwan van Beurden, and Eric W. Scharpf

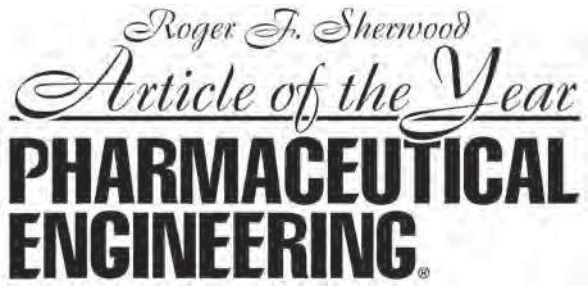
November/December 2008, Volume 28, Issue 6
Evaluation of Electron Beam (E-Beam) Sterilization Technology for Filling of Drug Products in Pre-Filled Syringes (PFS)
by Xiaogang Pan, Xiangning Deng, Michael Lee, Thomas O'Sullivan, Edwin Torres, Adrian Distler, and Narinder Singh

January/February 2009, Volume 29, Issue 1
Online Total Organic Carbon (TOC) as a Process Analytical Technology for Cleaning Validation Risk Management
by Keith Bader, John Hyde, Peter Watler, and Amber Lane

March/April 2009, Volume 29, Issue 2
PAT and Green Chemistry: The Intersection of Benign by Design and Quality by Design
by Dr. Berkeley W. Cue, Dr. John Berridge, and Julie B. Manley

May/June 2009, Volume 29, Issue 3
The FDA's Draft Process Validation Guidance – A Perspective from Industry
by Nuala Calnan, Alice Redmond, and Stan O'Neill

July/August 2009, Volume 29, Issue 4
Amplified Media Circulation – A New Way for Enhanced Sterilization Cycles
by David A. Karle, Gerald McDonnell, and Teppo Nurminen



Architects, Engineers – Constructors

CRB Consulting Engineers, 7410 N.W. Tiffany Springs Pkwy., Suite 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

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.

Cleanroom Products/Services

AES Clean Technology, 422 Stump Rd., Montgomeryville, PA 18936. (215) 393-6810. See our ad in this issue.

Dust Collectors

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

Employment Opportunities

Validation Specialist

SNC-Lavalin, Inc. seeks a Validation Specialist to test pharmaceutical equipment on various projects based out of Exton, Pennsylvania. Bachelor of Science in Mechanical Engineering required. Two years experience in job offered or in molecular science and/or biochemical research required. Travel to client facilities is required. Fax resume to HR Manager at 610-524-2443.

Employment Search Firms

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

Instrumentation

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

Passivation and Contract Cleaning Services

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

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

Processing Systems

GEA Process Engineering, 9165 Rumsey Rd., Columbia, MD 21045. See our ad in this issue.

Rupture Discs

Fike Corp., 704 SW 10th St., Blue Springs, MO 64015. (816) 655-4546. See our ad in this issue.

Sterile Products Manufacturing

Process Tek - *Sterility by Design*
INNOVATION, RELIABILITY & PROFESSIONALISM
R&D, Validation, GMP Auditing,
HACCP, Problem Solving and Training
for sterile products, packages & processes
Kailash S. Purohit, PhD
www.processtek.net • kaipurohit@processtek.net

Tanks/Vessels

Lee Industries, PO Box 688, Philipsburg, PA 16866. (814) 342-0470. See our ad in this issue.

Validation Services

Commissioning Agents, Inc., 1515 N. Girls School Rd., Indianapolis, IN 46214. (317) 710-1530. See our ad in this issue.

Valves

Gemu GmbH & Co., Fritz-Mueller-Str. 6-8, D-74653 Ingelfingen, Germany. +49 7940123-0. See our ad in this issue.

Water Treatment

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

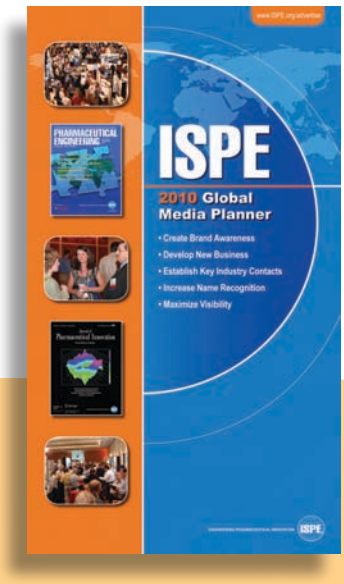
MECO, 12505 Reed Rd., Suite 100, Sugar Land, TX 77478. (800) 421-1798. See our ad in this issue.

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

JIM CRUMPLEY & ASSOCIATES
Pharmaceutical Recruiting Specialist
Put our expertise to work for you in:

- Facilities
- Process
- Automation
- Project
- Validation
- Quality Engineering

1200 E. Woodhurst Drive, B-400 • Springfield, MO 65804
Phone: 417-882-7555 Fax: 417-882-8555
E-mail: recruiter@crumpleyjobs.com
Web site: www.crumpleyjobs.com
We've been getting results since 1977!



Now Available!

ISPE
2010 Global Media Planner

For advertising, exhibit, and sponsorship opportunities, call ISPE Sales Executive, North America, Dave Hall at +1-813-960-2105.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

2008-2009 *Pharmaceutical Engineering* Article of the Year Finalists

We are pleased to announce the 2008-2009 Roger F. Sherwood Article of the Year Award Finalists. The winner will be selected from this group and recognized at ISPE's 2009 Annual Meeting.

September/October 2008, Volume 28, Issue 5
Functional Safety in the Life Science Industries
by David Hatch, Iwan van Beurden, and Eric W. Scharpf

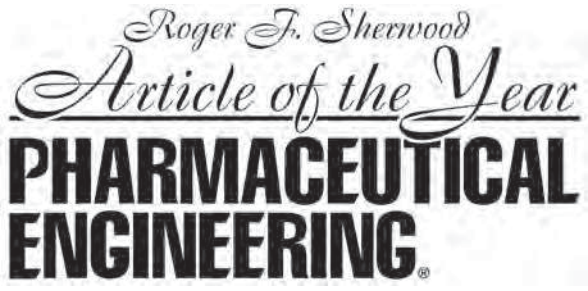
November/December 2008, Volume 28, Issue 6
Evaluation of Electron Beam (E-Beam) Sterilization Technology for Filling of Drug Products in Pre-Filled Syringes (PFS)
by Xiaogang Pan, Xiangning Deng, Michael Lee, Thomas O'Sullivan, Edwin Torres, Adrian Distler, and Narinder Singh

January/February 2009, Volume 29, Issue 1
Online Total Organic Carbon (TOC) as a Process Analytical Technology for Cleaning Validation Risk Management
by Keith Bader, John Hyde, Peter Watler, and Amber Lane

March/April 2009, Volume 29, Issue 2
PAT and Green Chemistry: The Intersection of Benign by Design and Quality by Design
by Dr. Berkeley W. Cue, Dr. John Berridge, and Julie B. Manley

May/June 2009, Volume 29, Issue 3
The FDA's Draft Process Validation Guidance – A Perspective from Industry
by Nuala Calnan, Alice Redmond, and Stan O'Neill

July/August 2009, Volume 29, Issue 4
Amplified Media Circulation – A New Way for Enhanced Sterilization Cycles
by David A. Karle, Gerald McDonnell, and Teppo Nurminen



more than engineering

"Vaccines are one of our industry's most critical tools for improving the world's health. I know how to make a difference by using my knowledge to help customers all over the world design vaccine production facilities which are flexible, optimised, and in compliance."

/ Klaus Hermansen

Klaus Hermansen

- International senior vaccine expert and top designer
- 25 years of experience in vaccine manufacturing and engineering

Special competences:

- Front end services and basic design
- Process and facility design
- Regulatory issues and workflow design

Consulting | Engineering | Construction | Validation | Solutions

To succeed in today's market, you require a focused partner created from industry DNA who can deliver a competitive advantage.
For more information on our vaccine know-how, please write to
contact@nnepharmaplan.com

nne pharmaplan®

nnepharmaplan.com

On-Line Exclusive Article
PHARMACEUTICAL ENGINEERING®
The Official Magazine of ISPE
September/October 2009, Vol. 29 No. 5

This article presents the provisions in the draft patent law for genetic resources, compulsory licensing of medicines, parallel importation, and the Bolar exception.

China Pharmaceutical Intellectual Property Protection Reform – Review of the Medicine-Patent Related Provisions in the "Draft Patent Law of the People's Republic of China"

by Dong Zuojun and Huang Wenlong

Introduction

The proposed changes to the Draft Patent Law indicate that the new provisions will have an impact on many global pharmaceutical companies. First, China will stringently control genetic resources and the cost of acquiring genetic resources will increase. Second, under some conditions, patented drugs will be copied compulsorily. Third, parallel importation will lower the price of the patented drugs in China. Fourth, the Bolar exception will bring generic drugs to the market quicker. This article attempts to clarify the changes and provide foreign pharmaceutical companies in or coming to China with the information they need to make educated business decisions.

Provisions Related to Medicine and Drugs in the Draft

There is a greater breakthrough in the draft version compared with the previous patent law in terms of obtaining patents for genetic resources-related medicine, compulsory licensing of medicines, parallel importation, and the Bolar exception in the development process, which will significantly impact the development of the pharmaceutical industry. It should be noted that the draft is submitted to the National People's Congress (NPC) by the State Council in accordance with legislative procedures of China. In other words, the draft has been accepted by the State Council. Depending on former legislative practice, the draft of the State Council will not be amended drastically by NPC, specifically in regard to genetic resources, licensing of compulsory of medicines, parallel importation, and the Bolar exception. The draft will become a law in the near future.

Provisions Related to Genetic Resources

It is stipulated in the second part of the draft that a new article would be added as Article 2 under the fifth provision of current patent law: "The patient rights will not be granted for any completion of invention relying on genetic resources that were obtained or used in violation of the relevant laws and administrative regulations."[1]

It is stipulated in the 14th part of the draft that the previous 26th provision would be changed into the 27th, adding another article as Article 6: "The applicant should state clearly the direct source of genetic resources and the original sources in his or her patent application file of the invention relying on genetic resources; if the applicant cannot affirm the original sources, he or she should make an explanation."[2]

Provisions Related to the Compulsory Licensing of Medicine

It is stipulated in the 17th part of the draft that another provision would be added in the current patent law as Provision 51: "For the purpose of public health, medicines granted patent in China can get compulsory licensing from the Patent Administration Department under the State Council of China to the manufacturing

and export to the following countries or regions: 1. The least developed countries; 2. Members who have not the capacity or are lack of the full capacity to manufacture medicines and drugs, and have already fulfilled the relevant procedures in accordance with World Trade Organization treaty the People's Republic of China has participated in."[3]

It is stipulated in the 19th part of the draft that another provision would be added in the current patent law as Provision 54: "In accordance with the current law, in addition to the medicines compulsory licensing stipulated in the 2nd article of the 49th provision and the 51st provision, the implementation of medicines compulsory licensing should be permitted to supply the domestic market."

Provisions Related to Parallel Importation and the Bolar Exception

It is stipulated in the 28th part of the draft that the first article in the 63rd provision would be changed into the 70th provision, in which the first item amended as: "either the patent product is made by the patentee or by any units or individuals under the permission of the patentee, or the sold patent product which is directly obtained in accordance with the process is to use, offer to sell, sell, import." (Annotation: this case was not regarded as infringement). One item was added as the fifth item: To provide the necessary information to administrative examination and approval, any unit or individual to manufacture patent drugs or patent medical equipment or devices." The Bolar Exception (also referred to as the FDA Exception) is the result of the American court case of Roche Products Inc. v. Bolar Pharmaceutical Co., 733 F.2d 858 (Court of Appeals for the Federal Circuit 04/23/1984), where the generic drug manufacturer intended to develop for sale a generic version of a patented drug that was manufactured and sold by Roche, before the expiration date of Roche's patent. The exception refers to a patent right that allows a third party to undertake, without the authorization of the patentee, acts in respect of a patented product that are necessary for the purpose of obtaining regulatory approval for a product. The following is how the exception is described in the American Patent Law 35 U.S.C. §271(e)(1): "it shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention… solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products."[18]

Analysis on the Impact of Genetic Resources-Related Provisions to *Medicine Patent*

Even though China is a member of the Convention on Biological Diversity (CBD), the current law system has not totally represented the three basic principles for biological genetic resources: "national sovereignty, prior informed consent, and benefit-sharing." As a result, the language suggested in the draft of the current patent law states, "to amend the current patent law to fulfill the convention offered rights."5 Therefore, the draft connects genetic resources to patent systems.

Draft Indicates that China will Strengthen Controls on Access to Genetic Resources

Stipulations in the second part in the draft of the patent law are related to access to genetic resources. The provisions stressed the legality of the access to or use of genetic resources in the process of inventions, which means it should be in line with laws and administrative regulations. "Law" and "administrative regulation" has special meanings in the Chinese legislation language.[6] The implied meaning of this provision is that China will further introduce special laws on the acquisition and use of genetic resources.

Control of Genetic Resources would Increase the Limit of the Cost to Acquire Medicine Patent

Medicine patent is always in close connection with genetic resources, and the latter is an important source of medicine patent. For example, medicine patent of many developed countries is from genetic resources of developing countries,[7] and developed countries become the largest holders of patent for genetic resources.[8] The draft of the patent law of China would make the acquisition of medicine patent related with genetic resources more difficult than before. This trouble can be embodied in the following examples.

China has just issued the new regulations on the control of genetic resources, which are the "Procedures for examination and approval of the entry and exit animal genetic resources and research and the use by foreign cooperation of People's Republic of China" (People's Republic of China State Council Decree No. 533) (hereinafter referred to as the procedures for examination and approval). From this, we can see the way China controls genetic resources, and also identify where the problems lie.

The control of "procedures for examination and approval" is reflected in the following areas:

- First, to ship the genetic resources outside of China should be approved by provincial authorities.[9]
- Second, qualify domestic partners of the genetic resources, which is limited to Chinese education and scientific research institutions or enterprises solely owned by the Chinese with legal personality.[10]
- Third, research cooperation between domestic and foreign institutions should be approved by provincial authorities.[11]

At the same time, "Procedures for examination and approval" emphasizes the function of country sharing the benefits of the program. No matter whether the genetic resource is shipped out or used to cooperate with foreign institutes, they should meet the reasonable requirements of the "benefit-sharing program by signing with foreign importers" and "national benefit-sharing programs."[12]

Information Disclosure Requirements do not Affect the Patent

In the draft, the genetic resources will differentiate the direct sources and the original sources. Understood literally, "direct sources" could be construed as a patent application with the closest source of genetic resources. The "original source" of genetic resources is the source of the original, this may not be the source of their own, or after it has changed many times to the patent applicants. In the patent application, the direct source must be described; and for the original source, if the case cannot be described, the "reasons" should be provided.

The author believes that the provision is flexible. Its purpose is to let the original holders of genetic resources know whether the genetic resources were being used and by whom. As a result, it makes a benefit balance between the direct genetic resources user and the original source holder since it requires patent applicants to disclose the information to the maximum without increasing its extra burden.

The Impact of Pharmaceuticals Compulsory Licensing and Parallel Importation Terms

The new compulsory license of the draft is to implement the provisions "Regarding 'Trade-Related Aspects of Intellectual Property Rights Agreement' and Public Health Declaration" as well as the World Trade Organization General Council "To amend 'Trade-Related Aspects of Intellectual Property Rights Agreement' protocol." Under the current Chinese Patent Law, compulsory drug licensing rights, due to the public health issue was maintained[13] in the draft the scope of the compulsory licensing was further expanded. This is a major role in terms of the settlement of the least developed countries, as well as drug production capacity of less than members of the WTO's public health problems. At the same time, according to the provisions of Article 19 in the draft, in that case, the drugs under compulsory licensing cannot be sold in China's domestic market. It is foreseeable that the terms do not have a direct impact to foreign direct established pharmaceutical companies in China, but will have an impact on the market in the compulsory licensing destination country, by reducing the local price of compulsory licensed medicines. This also is in line with China's own practical needs. At present, there are more than 6,300 pharmaceutical companies in China, many of which are faced with the problem of excess production capacity. The draft will further expand Chinese pharmaceutical enterprises drug production scope, which will make full use of China domestic production capacity.

If the newly-increased compulsory licensing article is in order to fulfill its international obligations in other countries to solve the drug problem, the parallel importation of drugs is the terms of China in order to solve its own problems. In China, the high drug prices have been the focus of attention of the public for a long time. Although the Chinese government has taken ongoing measures to control drug prices, brand drug prices of foreign pharmaceutical companies in China are still high. The draft makes the provisions of the parallel importation of patented drugs no longer regarded as infringement, based on the experience in other countries,[14] this will make China's domestic prices of foreign brands drugs decrease significantly.

Bolar Exception will be More Beneficial to the Generic Drug Manufacturer

The draft stipulates that to produce patented drugs or patented medical equipment to provide the necessary information for the purpose of administrative approval would not be considered infringement. China produces generic drugs to meet the needs of national health; more than 90% of essential drugs in China rely on imitation, 83% of western medicine patents are from abroad.[15] The current actual situation make it necessary for China to take measures to protect and encourage the production of generic drugs in China, the Bolar exception of the draft will definitely be an appropriate policy for Chinese pharmaceutical industry.

Compared with other countries, China's Bolar Exceptions have its own characteristics. First, medical devices are included clearly. This also is consistent with the United States.[16]

Second, there are less restrictive conditions for the "Bolar Exception." There are more restrictive conditions in terms of Bolar Exception in some countries, instead, there is not so much in China. It doesn't matter whether it's for commercial purposes or only limited to the laboratory production, the only point is that it's for the purpose of the administrative approval.

Third, the patent protection period cannot be extended. According to the U.S. Hatch Waxman's case, the patent protection period will be extended to compensate for the patentee if the FDA' s approval takes a very long time. However, there is no article in terms of patent medicines or medical devices of the patent protection period added in the draft, which shows that China is intended to provide more benefit to the public compared with the patentee.

Fourth, the approval procedures of medicines or medical devices by the Chinese SFDA will be impacted by the draft's Bolar Exception. Based on China's current "Drug Registration Procedures," when there is any patent dispute, the SFDA will suspend the approval procedure upon receiving the court decision.[17] It is the author's opinion that the Bolar Exception of the draft will help reduce the number of suspensions and the drug applicant's submission will go smoothly.

In other words, those new changes of the patent law make the foreign pharmaceutical companies face more and more challenges. The cost of acquiring genetic resources will increase; patent drug will no longer be monopolized under some conditions; the price of the patent drug will be reduced, and the generic drug will be brought to market faster. The one and only measure the pharmaceutical companies should do in response to the new changes is to acclimatize oneself to it and be better prepared.

References

1. Patent law amendment of People's Republic of China (Draft), 2nd, http://www.npc.gov.cn/huiyi/lfzt/zlfxzaca/2008-08/29/content_1447395.htm, log on 13 November 2008.

2. Patent law amendment of People's Republic of China (Draft), 14th, http://www.npc.gov.cn/huiyi/lfzt/zlfxzaca/2008-08/29/content_1447395.htm, log on 13 November 2008.
3. Patent law amendment of People's Republic of China (Draft), 17th, http://www.npc.gov.cn/huiyi/lfzt/zlfxzaca/2008-08/29/content_1447395.htm, log on 13 November 2008.
4. Patent law amendment of People's Republic of China (Draft), 28th, http://www.npc.gov.cn/huiyi/lfzt/zlfxzaca/2008-08/29/content_1447395.htm, log on 13 November 2008.
5. The explanation part of patent law amendment of People's Republic of China, (Draft), http://www.npc.gov.cn/huiyi/lfzt/zlfxzaca/2008-08/29/content_1447395.htm, log on 13 November 2008.
6. In China, the law can only be constituted by the National People's Congress and National People's Congress Standing Committee, administrative regulation can only be constituted by the States Council. Legislation Law of the People's Republic of China, 7th, 56th, http://www.dffy.com/faguixiazai/xf/200311/20031111130229.htm, log on 13 November 2008.
7. Wei, Y., The Impact to Foreign Investment of China Heredity Legislation, *The Rule of Law Forum,* November 2007, Vol. 22, No. 6, p. 63.
8. George, J., van Staden, J., Intellectual Property Fights: Plants and Phyto-rmedicinals – Past History, Present Scenario and Future Prospects in South Africa, *South African Journal of Science,* August 2000, Vol. 96, p. 433.
9. Procedures for Examination and Approval of the Entry and Exit Animal Genetic Resources and Research and the Use by Foreign Cooperation of People's Republic of China, (People's Republic of China State Council Decree No.533), 7th, http://www.gov.cn/zwgk/2008-09/04/content_1087573.htm, log on 13 November 2008.
10. Procedures for Examination and Approval of the Entry and Exit Animal Genetic Resources and Research and the use by Foreign Cooperation of People's Republic of China, (People's Republic of China State Council Decree No. 533), Article 6 of Section 8, http://www.gov.cn/zwgk/2008-09/04/content_1087573.htm, log on 13 November 2008.
11. Procedures for Examination and Approval of the Entry and Exit Animal Genetic Resources and Research and the use by Foreign Cooperation of People's Republic of China, (People's Republic of China State Council Decree No.533), 9th, http://www.gov.cn/zwgk/2008-09/04/content_1087573.htm, log on 13 November 2008.
12. Procedures for Examination and Approval of the Entry and Exit Animal Genetic Resources and Research and the use by Foreign Cooperation of People's Republic of China, 6, 7, 8, 9th, http://www.gov.cn/zwgk/2008-09/04/content_1087573.htm, log on 13 November 2008.
13. Patent Law of People's Republic of China, 49th, http://www.people.com.cn/item/flfgk/rdlf/1992/111404199221.html, log on 13 November 2008.
14. Yu, X., Wu, L., Demonstration Analysis of Parallel Importation in Sweden and Inspiration to China, *Science Research Management,* Vol. 28,No.1, January 2007, pp.146-154.
15. Na, L., He, Z., Wang, Y., WTO and Public Health, [M], Beijing, Publishing Company of Qinghua University, 2005: 261-262.
16. Eli Lilly and Co. v. Medtronic, Inc., 496 U.S. 661, (1990).
17. Drug Registration Procedures, (State Food and Drug Administration Degree No. 28), 18th, http://www.sda.gov.cn/WS01/CL0053/24529.html, log on 13 November 2008.
18. The Bolar Exception in China and the Latest Legislature Developments, http://www.chinalawandpractice.com/article/1968094/, log on 3 June 2009.

About the Authors

Dong Zuojun is currently pursuing his Doctorate degree in social and pharmacy administration at China Pharmaceutical University, where he also completed four years of undergraduate studies and three years of postgraduate studies. Zuojun acquired his MS in chemistry and Master's degree in pharmaceutical management. He is currently an officer of the Food and Drug Administration of Zhejiang province, China. He is responsible for the GMP audit and pharmaceutical product permission. He has worked in Zhejiang FDA for seven years and has extensive experience in pharmaceutical policy research and supervision. Prior to becoming a government official, Zuojun worked at the Zhongyang pharmaceutical company for seven years, was involved with pharmaceutical production for more than three years, and marketing for more than four years. He can be contacted by telephone: 0086-0571-88903352 or by email: jzd1970@163.com.

Huang Wenlong is chemical professor, doctoral tutor, director of Science and Technology section and deputy director of New Drug Research Center in China Pharmaceutical University, member of the expert committee of National New Drug Research and Development Leading Group, member of the National and Jiangsu provincial drug assessment committee, member of the State Committee for Review of New Drug Fund, member of the Sino-French Youth Pharmaceutical Chemistry Prize Review Experts Committee, executive editor of "Chinese New Drugs Journal," "Pharmacy Progress," "China Pharmaceutical University Journal," "Chinese Pharmacy Chemistry Journal" and "Chinese Medical Technology and Market." Academic training, he earned his Doctorate degree in chemistry from China Pharmaceutical University and engaged in post-doctoral study at Strathclyde University in Britain. He mainly engaged in pharmaceutical chemistry teaching and research on Design and Synthesis of Drugs and structure-activity relationship research. He has worked in this field for more than 30 years and issued hundreds of papers in domestic and overseas science publications. He can be contacted by telephone: 0086-025-83271480 or by email: ydhuangwenlong@126.com.

China Pharmaceutical University, School of International Pharmaceutical Business, Tong jia lane 24, Nanjing, Jiangsu, 210009 China.

The Global Information Source for Pharmaceutical Science and Manufacturing Professionals

PHARMACEUTICAL ENGINEERING®

THE OFFICIAL MAGAZINE OF ISPE

SEPTEMBER/OCTOBER 2009 VOLUME 29, NUMBER 5

Strategic Planning for Outsourcing

Managing Offshore Outsourcing

Quality Risk Management

Building Information Modeling

Process Monitoring and Control

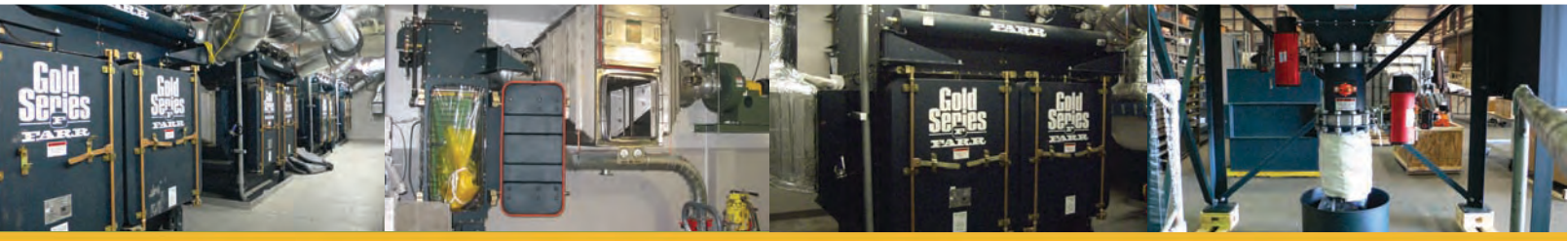
Global Sourcing Logistics

Interview with Bob Best, ISPE President and CEO

Dust Problem?

Go to where dust and fume pollution meet permanent solutions.

www.pharmadustcollectors.com



We make the toughest, best-built industrial dust collectors in the industry!

Visit www.farrapc.com today.

FARR®
Air Pollution Control

camfil FARR

Farr APC is a proud member of the Camfil Farr Group.
Visit www.camfilfarrapc.com for offices out of North America.

866-530-5474
Jonesboro, AR • email: filterman@farrapc.com

What Does the Future of Your Facility Look Like?

CRB's FutureFacility℠ can bring it into focus.

Whether you are building a new facility or updating an existing one, CRB can provide insight into how new technologies and construction methods, closed processing techniques, lean thinking and new compliance strategies can be used to produce innovative design concepts that significantly reduce facility complexity, capital investment, energy consumption, project schedules and cost of goods.

CRB is a global provider of end-to-end solutions for life science and advanced technology companies. Our solutions deliver enhanced value, productivity and return on investment. Whether you are across town or across the pond, CRB's consulting, design and construction expertise will meet your R&D and manufacturing needs, while adding some black to your bottom line.

1.877.4CRBUSA
crbusa.com

To find out more about how CRB's FutureFacility℠ program can bring your facility requirements into focus, visit www.crbusa.com/futurefacility

Consulting Design Construction Commissioning Qualification

The Global Information Source for Pharmaceutical Science and Manufacturing Professionals

PHARMACEUTICAL ENGINEERING®

THE OFFICIAL MAGAZINE OF ISPE

SEPTEMBER/OCTOBER 2009 VOLUME 29, NUMBER 5

PHARMACEUTICAL ENGINEERING®
(ISSN: 0273-8139) is published bimonthly by ISPE, 3109 W. Dr. Martin Luther King Jr. Blvd., Suite 250, Tampa, Florida 33607, USA. Telephone +1-813-960-2105. Fax +1-813-264-2816. Periodicals postage paid at Tampa, Florida, USA.

BPA Worldwide

Subscriptions.
An annual subscription to PHARMACEUTICAL ENGINEERING is included in the membership of ISPE.

US Postmaster:
send change of address to Pharmaceutical Engineering, 3109 W. Dr. Martin Luther King Jr. Blvd., Suite 250, Tampa, Florida 33607.

Canada Postmaster:
send change of address information and blocks of undeliverable copies to PO Box 1051, Fort Erie, ON L2A 6C7. Canada Post Agreement Number 40041350.

ISPE HEADQUARTERS
3109 W. Dr. Martin Luther King Jr. Blvd.
Suite 250
Tampa, Florida 33607 USA
Tel +1-813-960-2105
Fax +1-813-264-2816

ISPE ASIA PACIFIC OFFICE
73 Bukit Timah Road
#04-01 Rex House
Singapore 229832
Tel +65-6496-5502
Fax +65-6336-6449

ISPE CHINA OFFICE
Suite 2302, Wise Logic International Center
No. 66 North Shan Xi Road
Shanghai 200041, China
Tel +86-21-5116-0265
Fax +86-21-5116-0260

ISPE EUROPEAN OFFICE
Avenue de Tervueren, 300
1150 Brussels, Belgium
Tel +32-2-743-4422
Fax +32-2-743-1550

www.ISPE.org

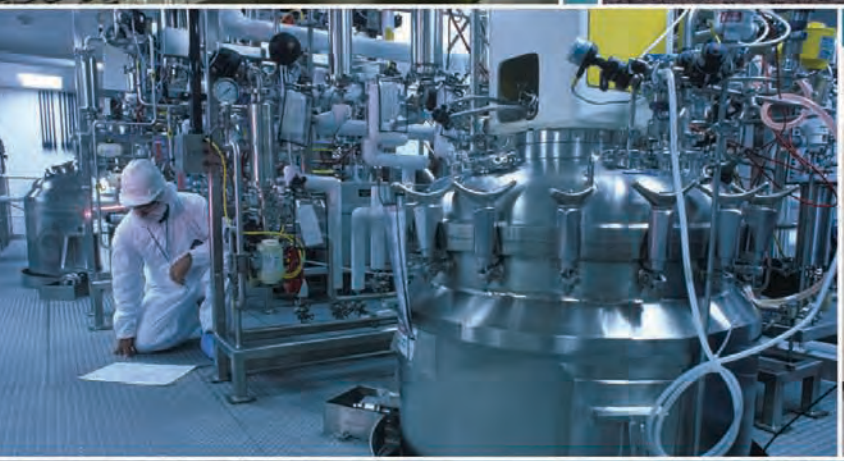
ISPE
ENGINEERING PHARMACEUTICAL INNOVATION

PARSONS

Integrated Solutions for the Global Life Sciences Industry

Engineering, Architecture, Procurement,
Program and Construction Management, Validation

Please visit us at booth #801 at the ISPE Annual Meeting



www.parsons.com 1.800.555.0532 LifeSciences@parsons.com

Table of Contents

The Global Information Source for Pharmaceutical Science and Manufacturing Professionals

PHARMACEUTICAL ENGINEERING®

THE OFFICIAL MAGAZINE OF ISPE

SEPTEMBER/OCTOBER 2009 VOLUME 29, NUMBER 5

Cover Design

Lynda Goldbach, ISPE Publications Manager

Current Issue/Theme

SEPTEMBER/OCTOBER 2009
Management of Globalization

Next Issue/Theme

NOVEMBER/DECEMBER 2009
Integrated Commissioning and Qualification

Publishes 20 November 2009

Articles

Departments

ISPE
ENGINEERING PHARMACEUTICAL INNOVATION

On-Line Exclusive Article

visit www.ISPE.org/PharmaceuticalEngineering

No matter what they throw at you, we've got you covered.

FDA
YOU HAVE TO COMPLY!
FORM 483
GLP/GMP
ISO STANDARDS
ANNUAL REPORTS
WARNING LETTER
ADVERSE EVENTS REPORTING
21 CFR
PART 11
PRESCRIPTION DRUG MARKETING ACT
ICH GCP AUDITS
CONSENT DECREE
QSR AUDITS
CLINICAL MONITORING
TRACEABILITY DOCUMENTATION

QPHARMA

22 South Street • Morristown, NJ 07960 • **888-742-7620** • **info@qpharmacorp.com** • **www.qpharmacorp.com**

This article presents key issues in regard to pharmaceutical contract manufacturing.

Trends in Pharmaceutical Manufacturing – Key Issues When Deciding to Outsource

by Takayuki Kasai

Introduction

The pharmaceutical industry contributes a significant amount of value to worldwide healthcare and the economy.

In spite of the challenges of a global economic crisis, the pharmaceutical manufacturing industry remains an important source of strength for the worldwide economy. The industry provides thousands of stable and high-quality jobs, contributes substantially to federal, state, and local tax bases, and creates technical innovations along with economic ripple effects that strengthen other economic sectors. On the other hand, the environment of the pharmaceutical manufacturing industry has been changing drastically in the last 10 years with strong competition, due to the decrease of new drug approvals, increased development costs, and stricter regulatory requirements. In order to sustain growth, it is clear that pharmaceutical companies need to act quickly and establish restructuring plans and visions that make full use of outsourcing effectively in the four key areas: 1. Research, 2. Development, 3. Manufacturing, and 4. Sales - *Figure 1*. Having a policy and a basic strategy for outsourcing is becoming a prerequisite for surviving the strong competition from rival companies. Among the four key areas, the manufacturing sector was inherently conservative for outsourcing although it was introduced some 20 years. Today, outsourcing has become a very popular practice for most of the pharmaceutical industry. Companies are making the competitive decision to increase business through strategic manufacturing partnerships, instead of in-house manufacturing.

The Contract Manufacturing Environment: Current and Future

It is no doubt that the contract manufacturing market size is directly influenced by the pharmaceutical market. The global pharmaceutical market in 2009 is estimated to reach $750 billion, down from the $820 billion forecasted in October 2008, reflecting both the lower growth rate and currency exchange fluctuations.[1] According to the IMS forecast, the growth rate for the global

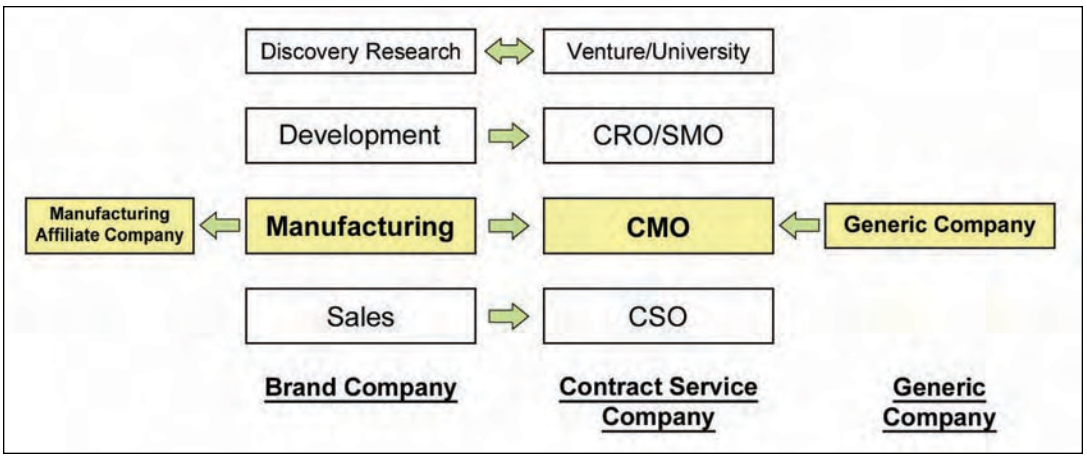


Figure 1. Four key areas for the pharmaceutical industry and the relationship to contract service companies.

Continued on page 10.

High performance teams make the difference.

Commissioning Agents, Inc.

Our teams are recognized industry leaders in developing better methods to meet your business and regulatory demands. When schedule is your problem, we are your solution.

Major services include:

- Commissioning planning, equipment start-up, troubleshooting, field execution, verification and qualification (IQ, OQ, PQ)
- Quality Risk Management (QRM) Implementation and Risk Based Qualification Programs
- Validation – Process, Cleaning, Sterilization, Computer
- Process Improvement Services: Process Analytical Technology (PAT), technology transfer, process improvement studies
- Technical services including design reviews, SOP development, and training
- Maintenance program development and implementation
- cGMP Compliance Services – audits, regulatory reviews, improvement projects, submission assistance, and comparability protocols

Achieve world class manufacturing.

Call Robert E. Chew, P.E., President
Robert.Chew@CAgents.com
+1.317.710.1530

CommissioningAgents.com

CAI

An Employee-Owned Company

"For some companies, the outsourcing of manufacturing functions has become first preference for new products where volumes are uncertain. The 10 to 12 percent growth per year of the US contract manufacturing market compared to that of the pharmaceutical market's one to two percent clearly shows this.[10]"

pharmaceutical market will continue to be three to six percent through 2013. This is assuming differing growth rates for each global region and regional differences of growth rate: one to five percent for the mature markets, which include the US – one to two percent; top five EU – three to four percent; and Japan – four to five percent, and 14 to 15 percent for China, Brazil, India, Korea, Mexico, Turkey, and Russia.[2] The following are key drivers that will contribute to the continuous growth of the pharmaceutical industry:

1. Increase in population (6.5 billion in 2005 to 7.6 billion in 2020) and rapid aging ratio over 65 years (7.3 percent in 2005 to 9.4 percent in 2020).
2. Advancement of clinical treatment and innovation in the pharmaceutical R&D sector.
3. Increasing demand for medicine or vaccines for new infectious diseases.
4. Investigation of the mechanism for various incurable diseases like Cancer or Alzheimer's.
5. Growth of the developing world market.
6. Global warming may affect healthcare in the world.[3]

On the other hand, what is the contract manufacturing market size at the moment? There are several articles that debate this question.[4,5,6,7] The articles state the size of the market to be between $17 to 38 billion in 2007; however, for the following reasons, the figures should be regarded as an estimate only. The first reason is that only a small portion of Contract Manufacturing Organizations (CMOs) are dedicated to contract manufacturing. Many contract manufacturers are fundamentally pharmaceutical companies that manufacture and sell their own products and offer contract manufacturing services in addition to their main core business. Because the majority of contract manufactures fall into this category, it is difficult to separate contract manufacturing revenue from main core business revenue within these companies. The second reason is that there are a number of pharmaceutical manufacturing processes [Active Pharmaceutical Ingredient (API) manufacturing, formulation, and packaging] that each combine further manufacturing steps. The number of processes and steps in addition to the complex in-house and outsourcing matrix make it extremely difficult for analysts to pinpoint revenues earned from contract manufacturing only.

The author's estimate for the contract manufacturing market in the fiscal year 2009 is shown below. Market share are Brand (89 percent) vs. Generic (11 percent), manufacturing costs against sales are Brand (25 percent) vs. Generic (50 percent),[8] outsourcing ratio is both Brand and Generic (24 percent).[9] The calculated result, $50 billion is relatively higher than the results shown in articles[4,5,6,7] The author concludes that the below market size is more plausible because an outsourcing ratio has been applied to compensate for potential outsourcing revenue that is not clearly reflected in financial results.

Brand: $750 billion×89%×25%×24%= $40 billion
Generic: $750 billion×11%×50%×24%= $10 billion
Total: $50 billion

In the meantime, what will happen for the pharmaceutical supply chain in the future? In the past, large pharmaceutical companies increased production capacity and relied heavily on employees to perform the manufacturing functions in-house, but this was when approval paths where predictable, there were fewer restrictions on reimbursement and high volume, and companies could reap high value for blockbuster drugs. Firms were able to extrapolate the volume of drugs into the future and invest hugely in new capacity. Today, due to much smaller development pipelines, fewer employees through corporate restructuring and mergers, the resources at large pharmaceutical companies have become exhausted and the use of third party service providers has become more cost effective. For some companies, the outsourcing of manufacturing functions has become first preference for new products where volumes are uncertain. The 10 to 12 percent growth per year of the US contract manufacturing market compared to that of the pharmaceutical market's one to two percent clearly shows this.[10] The majority of the global pharmaceutical industry is now expanding their supplier management functions to ensure that third party contractors are properly controlled and monitored in place of performing manufacturing in-house.

Service Scope of the Contract Manufacturer

At present, it takes more than 10 years to launch a prescription drug with costs averaging $1.2 billion to $1.3 billion for blockbuster type products.[11] The risks associated with bringing a drug product to market are extremely high with only 0.01% of all drug candidates actually being approved. Formulation and manufacturing issues may arise making it difficult to produce a certain compound, unforeseen side affects may force the pharmaceutical company to terminate clinical trials, or development costs may be too excessive and recuperation of development costs may be impossible within the patent protection period. In most pharmaceutical companies, manufacturing had traditionally been undervalued compared to R&D and sales and marketing functions. R&D may be thought to harbor the bright scientists who have the companies long term future in their hands, while sales and marketing's powered-up sales force bring in the money.

Continued on page 12.

Pharmaceutical Processing Systems

GEA Pharma Systems supplies the world's pharmaceutical companies with state-of-the-art solutions for the processing of active pharmaceuticals, ranging from the processing of API (Active Pharmaceutical Ingredient) to the production of solid dosage forms and sterile liquids finishing.

The GEA Pharma Systems portfolio of leading industry brands includes:

- Aeromatic– Fielder and Collette granulation/drying systems
- Buck contained materials handling systems
- Courtoy advanced tablet presses
- Niro spray drying technology
- Lyophil freeze drying systems including automatic loading and unloading

The combination of these strong brands with a deep commitment to research and development has resulted in GEA Pharma Systems establishing a leading global market position.

Engineering Excellence.

GEA Pharma Systems

9165 Rumsey Road • Columbia, MD 21045
Tel 410 997 7010 • Fax 410 997 5021
E-mail info@niroinc.com • Website www.niroinc.com

"Through this new ideology, manufacturing has begun to shift from what used to be considered a "cost center" to a "profit center." It is evident that the development of CMC within a company is not only vital to successfully advance to commercial production, but it also is a key factor for the success of pharmaceutical development..."

Manufacturing, on the other hand, has always consumed a lot of money and has often been titled a 'cost center.' However, recently a number of serious and well-publicized production problems and launch delays in conjunction with a number of FDA initiatives that focus on manufacturing and its importance have enticed many pharmaceutical companies to introduce major changes in the way they interface R&D and sales/marketing with manufacturing. Specifically, it is recognized that Chemistry and Manufacturing Controls (CMC) contributes to a more stable supply, higher quality, and cost reduction not only during the process development stages, but also throughout the entire product life cycle.

A robust production development system on many occasions can bring about breakthrough for R&D activities. One example of a breakthrough that may be achieved is an improvement in dissolution or stability for material with bad physico-chemical properties (water insolubility and solid state instability). Another, is in the chemical process development area where there also are many cases where the process chemist is assigned to establish a scaled-up manufacturing process despite the fact that the process may be considered impossible to achieve for safety, environmental, and cost efficiency reasons at the final commercial size manufacturing stage. Moreover, through the employment of CMC, increased product value during the product's lifecycle can be achieved through the introduction of orally disintegrating and sustained release formulation techniques and other additional dosage formulations resulting in the maximization of product value.

Through this new ideology, manufacturing has begun to shift from what used to be considered a "cost center" to a "profit center." It is evident that the development of CMC within a company is not only vital to successfully advance to commercial production, but it also is a key factor for the success of pharmaceutical development in areas of material supply for pre-clinical and clinical trials, process development, stability analysis, quality assurance, etc. Due to the wide scope in which CMC activities can be applied, the contract manufacturing business also has expanded to offer clinical supply and development services over and above commercial production. This is becoming a strategic area for contract manufacturers and will continue to become an essential part of their service

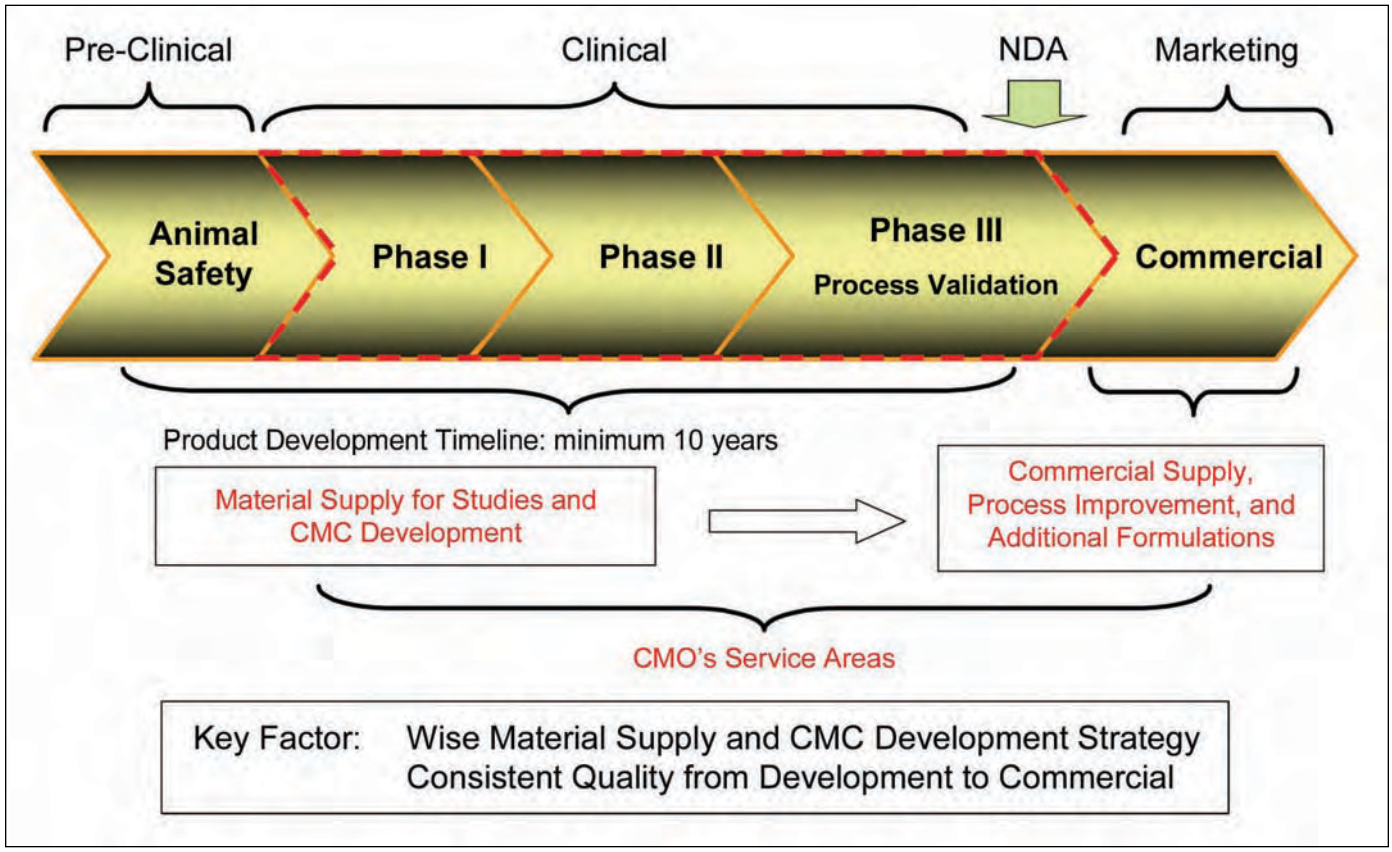


Figure 2. Product life cycle and CMO's service areas.

Continued on page 14.

With Siemens, cost-effective solutions are just the tip of the iceberg.

Siemens Water Technologies provides the largest portfolio of innovative solutions that get below the surface of all your plant's needs. Our reduction, reclaim and reuse approach helps your plant's water and energy conservation efforts, drastically reducing costs and waste production while meeting ever-increasing regulations. And with the most validated and non-validated pharmaceutical installations around the globe, experienced service teams, and fully functional factory acceptance tests (FAT), product safety and reliability are ensured, and profitability is maximized. Count on Siemens to provide more than just the tip of the iceberg. For more information, call 800.875.7873 ext. 5000 or visit **www.siemens.com/iceberg**

Answers for industry.

SIEMENS

scope in the years to come. Figure 2 illustrates the product lifecycle and service areas where contract manufacturers can currently assist pharmaceutical companies.

It is only a very recent trend for contract manufacturers to contribute to the entire value chain (API, formulation, product development and manufacturing, packaging and distribution). One of the essential factors for contract manufacturers is the ability to offer compliance with Good Manufacturing Practices (GMPs) for all manufacturing processes after the introduction step of a starting material as described in ICH-Q7, which is recognized as a common global standard. In addition, even though GMP is not required for the earlier manufacturing steps, i.e., raw materials, excipient, and packaging material, it is generally required suitable quality management (QA/QC) to ensure the quality impact to the finished product - *Figure 3*.

Outsourcing Policy and Strategy

Prior to selection of a contract manufacturer, it is in the pharmaceutical company's best interest to have first and foremost a clear outsourcing policy and strategy. Without this, benefits derived from outsourcing can easily be diminished. By establishing a clear outsourcing policy and strategy, it is important to recognize what the companies' core competences are and to possess a good understanding of current and future resources within the company (human, material, money, and in-house information) and be able to identify where outsourcing may be best utilized for existing product lines and development pipelines.

Good examples of companies that are very forward thinking when it comes to outsourcing are venture capitalist companies. These companies are largely unable to perform manufacturing functions in-house and establish comprehensive business models that focus on discovery and research activities, as well as early clinical trials up to Phase I and II [up to the Proof of Concept study (POC)] before licensing. Venture capitalists tend to concentrate their efforts on small scale API synthesis and research for other back-up and follow-up compounds in their research laboratories and rely heavily on contract manufacturers to handle process development and material supply in accordance with GMP.

Pharmaceutical companies, which are able to perform all functions (discovery, clinical development, CMC research, and commercial manufacturing) in-house, also can benefit by taking a case-by-case approach to outsourcing. Table A shows a model approach for API outsourcing. These companies must consider their current and future resources in respect to all the steps during the entire product lifecycle and determine a strategic plan for the future. The outsourcing of kg scale synthesis is not included in this table; however, there also is a growing trend to outsource this type of work.

Reasons for performing critical manufacturing steps in-house may be attributed to the following reasons: 1. consistency of quality, 2. protection of confidential information, 3. cost reduction benefit through process improvement and breakthrough, and 4. technology/know-how transfer in-house. In the case where a pharmaceutical company regards technological information to be a key factor, case 1 or 2 may be

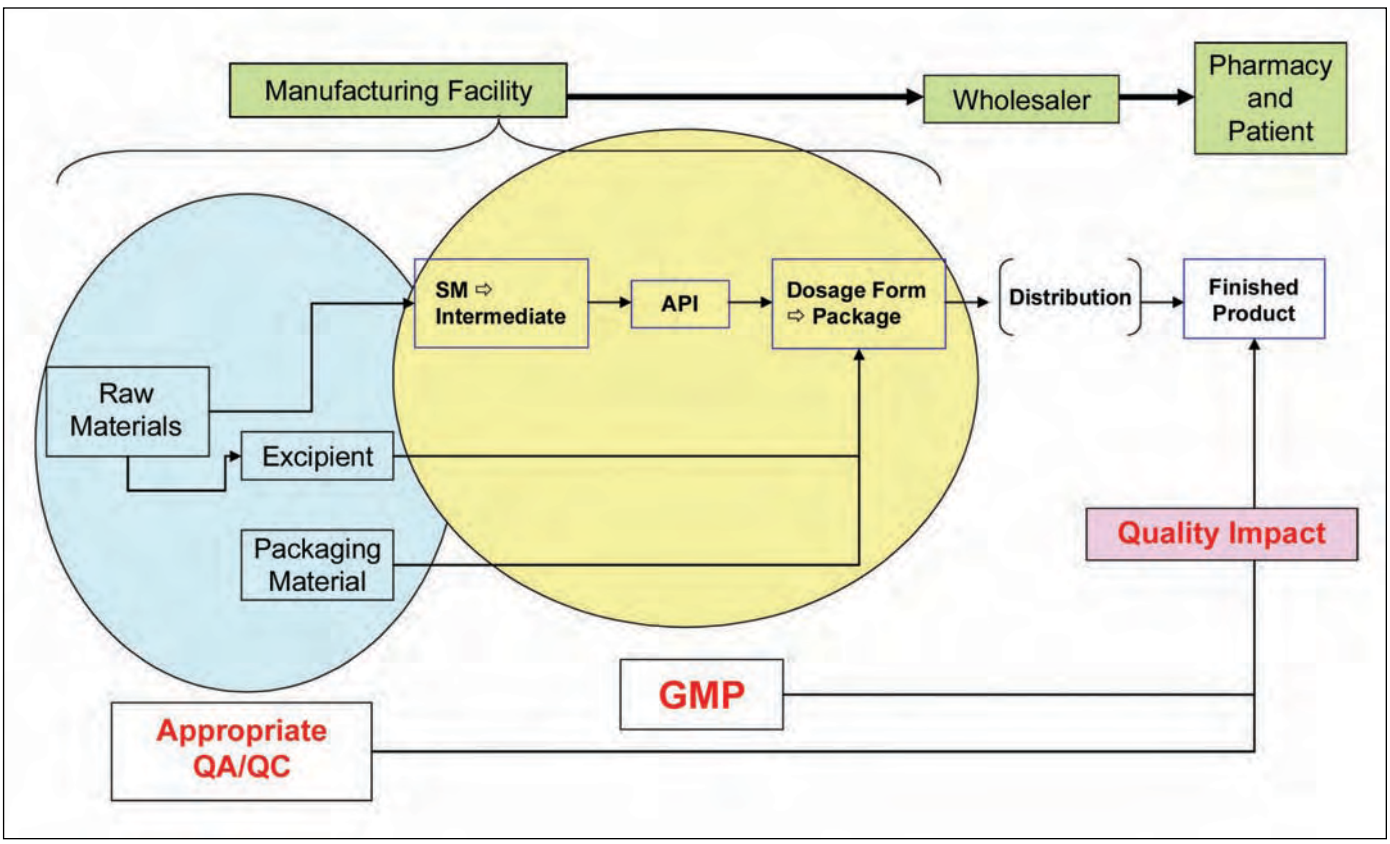


Figure 3. Supply chain of pharmaceutical products and quality requirement.

Continued on page 16.

HiProTect. Our Solution – Your Protection.

BOSCH
Invented for life

Handling highly potent products is difficult, we have the solution.

The GKF HiProTect 1700 is the industry's first true containment capsule filler for production-scale capsule filling and the first in a family of containment capsule fillers from Bosch Packaging Technology.

As drugs become more potent and regulations become more stringent, a way to separate the operator from the production area becomes increasingly important for manufacturers to consider. SMEPAC testing confirms that the HiProTect capsule fillers from Bosch offer the highest level of operator and facility safety in the industry when dealing with toxic compounds. This is achieved by incorporating a barrier system directly on the machine.

Extensive gowning is a time-consuming and expensive process, and does not ensure 100% safety. Personnel precautions can be significantly reduced when using a HiProTect machine from Bosch, thanks to the containment features built into the machine. This makes extensive PPE a thing of the past! Operators enjoy an ergonomically friendly work environment without the risk of exposure to the product.

The HiProTect maintains its integrity during both production and the automated wash down cycle. The production environment maintains a negative pressure to prevent product from escaping the system and contaminating the filling suite. A monitoring system is used to ensure proper air flow and under-pressure for containment.

Our Containment Specialists are ready to discuss your individual containment requirements and provide the customized HiProTect solution that will keep you at the leading edge of potent product handling.

Robert Bosch Packaging Technology, Inc.
Phone: +1 763 424 4700
sales@boschpackaging.com
www.boschpharma-us.com

Life Cycle	Manufacturing Step	Case 1	Case 2	Case 3	Case 4	Case 5
Pre-clinical	All Steps	In	In	In	In	In
Clinical (Ph1-Ph2)	Non-Critical Steps	In	In	Out	Out	Out
Clinical (Ph1-Ph2)	Critical Steps	In	In	In	In	Out
Clinical (Ph3)	Non-Critical Steps	In	Out	Out	Out	Out
Clinical (Ph3)	Critical Steps	In	In	In	Out	Out
Commercial (until peak sales)	Non-Critical Steps	In	Out	Out	Out	Out
Commercial (until peak sales)	Critical Steps	In	In	In	Out	Out
Commercial (peak sales to end)	Non-Critical Steps	Out	Out	Out	Out	Out
Commercial (peak sales to end)	Critical Steps	In	In	Out	Out	Out
Key: In-House: In Outsource: Out						

Table A. Case Study for API contract manufacturing during the product life cycle.

selected. If quality is regarded to be a key factor, case 3 or case 4 may be selected. It also is a possibility to select case 5; however, in doing so, it will become extremely important for a pharmaceutical company to select a reliable contract manufacturer that can ensure technological know-how, quality and confidentiality, and provide manufacturing consistency from development stages through to commercial stages.

All products have different supply volumes during the various stages of the product lifecycle. It is vital for pharmaceutical companies to perform capacity planning and production volume simulations and adjustment for development stages, as well as early, peak, and late commercial stages to determine the manufacturing site. It also is wise to determine several potential manufacturing sites. In the case of solid dosage forms, another factor needing to be considered is formulation change. Unlike a change in the API manufacturing process where changes are limited mostly to volume, it is not unusual for a formulation change to take place during development and/or commercial stages that requires an investment of new equipment, facilities, or even a new manufacturing site. For this reason, a very carefully thought-out and flexible strategy that involves a number of potential manufacturing sites including in-house manufacturing should be considered.

There also are growing instances where pharmaceutical companies do not possess the necessary technology, equipment, or facilities to perform formulation development and therefore this work is outsourced. Typical cases of this are simple formulations like suspensions and capsule filling of API for Phase I, and granule formulation design for the Japanese market for a product already sold internationally as a tablet.

In addition to the above, for solid dosage forms, it is necessary to have a good understanding of regional requirements as well. The color and size of a tablet marketed internationally may not be suitable for the Japanese market. There also may be differences in what determines a quality product versus a non quality product between different regions. Many international pharmaceutical companies struggle with the quality level applied here in Japan and the scrutiny to which product is inspected. The Japanese market has seen an average of 10 product recalls each year for the past 10 years because of biological foreign matter contamination in the way of hair, insects, and blood in the final product. In Japan, contamination of even a single hair in a lot size of 10 million tablets will be subject to a recall, unless it can be proven that the hair can be traced to only a limited portion of the lot. Foreign materials in blisters, small breakages, and wrinkles of packaging materials also are grounds for complaints.

While there may be huge financial benefits of manufacturing for the entire global market at a single site, it is extremely important to keep in mind the requirements for each of the markets being serviced. You may actually find that a lot of time and resources are being spent to maintain a cosmetic quality that is appropriate for the Japanese market and that it may actually be cheaper to manufacture or package in the Japanese market. In many instances, while manufacturing of bulk may be performed at a single international manufacturing facility, a packaging site may be employed locally due to language issues and regional preferences for packaging materials. In most cases, this is still the case with clinical trial packaging. There may be specific preferences for packaging materials and distribution used in trials between each country. For this reason, it is often important to secure several packaging sites in the countries where the trials will be conducted.

When deciding to outsource any of the formulation, manufacturing, or packaging steps during the products lifecycle, a key factor for success is to establish several contract manufacturing candidates and clearly define their strengths and weaknesses in regard to quality assurance, capacity, and speed.

Contract Manufacturer Selection

When selecting a contract manufacturer, the key areas to consider are: who and what to outsource, the extent in which to outsource (what stages of the product lifecycle), and how much volume. Data collection of potential contract manufacturer capabilities and capacities and information about in-house capabilities also are a crucial piece to the puzzle. Other areas to consider are: facility design, cost, quality (including regulatory inspection history), manufacturing technology, communication, Environment and Health and Safety (EHS)

Continued on page 18.

Innovation
makes it possible

Telstar Life Science solutions is constantly innovating to offer tailor-made solutions in high technology equipment for the pharmaceutical, biotech and related industries.

With over 45 years of experience and an international presence in more than 100 countries, Telstar is your partner to provide solutions in the following technologies:

Telstar ACE

High Containment Isolators

Telstar Celester

Sterilization Systems, WFI & Pharmaceutical Steam Generation Systems

Telstar Lyo

Freeze Drying Systems

Containment Systems
- Isolators
- Restricted Access Barrier Systems (RABS)
- Downflow booths

Sterilization Systems
- Moist heat sterilization autoclaves
- Chemical agent sterilization autoclaves
- Sterilization and depyrogenation ovens

WFI & Pharmaceutical Steam Generation Systems
- Multiple/simple effects stills
- Pure steam generators

Freeze Drying Systems
- GMP production freeze dryers
- Laboratory freeze dryers
- Loading & unloading systems
- Lyophilization support services

Laminar Air Flow Systems
- Laminar flow benches
- Biosafety cabinets
- Laminar flow booths
- Customized cabinets

Drying Systems
- Hot air drying
- Vacuum drying

Telstar®
Life Science solutions

TELSTAR LIFE SCIENCES
Josep Tapioles 120
08226 Terrassa (Spain)
T. +34 937 361 600
F. +34 937 859 342
sales.pharma@telstar.eu

TELSTAR NORTH AMERICA
1504 Grundy's Lane,
Bristol, PA 19007 (USA)
T. +1 215 826 0770
F. +1 215 826 0222
telstar.na@telstar.eu

Criteria	Weight	Company A		Company B		Company C	
		Rating	Score	Rating	Score	Rating	Score
Cost of Goods	9	5	45	3	27	5	45
Initial Investment	7	5	35	4	28	2	14
Quality Standard	10	5	50	4	40	3	30
Regulatory Inspection History	9	4	36	2	18	3	27
Capacity for Lifecycle	7	5	35	3	21	3	21
Technology Transfer Capability	8	4	32	3	24	3	24
Timeline for Implementation	10	4	40	3	30	3	30
Site Logistics	6	3	18	5	30	4	24
Communication	8	4	32	3	24	3	24
Confidentiality	9	4	36	4	36	4	36
EHS Management	8	5	40	4	32	3	24
Composite Score			399		310		299

Table B. Example of API manufacturing site decision.

Criteria	Weight	Company X		Company Y		Company Z	
		Rating	Score	Rating	Score	Rating	Score
Cost of Goods	8	4	32	3	24	5	40
Initial Investment	7	3	21	3	21	3	21
Quality Standard	10	3	30	4	40	5	50
Regulatory Inspection History	9	2	18	3	27	4	36
Capacity for Lifecycle	7	3	21	3	21	4	28
Technology Transfer Capability	8	3	24	5	40	4	32
Timeline for Implementation	9	3	27	4	36	5	45
Site Logistics	10	3	30	4	40	5	50
Communication	8	4	32	3	24	5	40
Confidentiality	9	4	36	4	36	4	36
EHS Management	7	3	21	4	28	4	28
Composite Score			292		337		406

Table C. Example of pharmaceutical manufacturing site decision.

management, confidentiality, capital, corporate culture, language, and people (knowledge) etc. An investigation process should be employed prior to the selection process and should be performed based on the guidelines set out in the outsourcing policy and strategy. In order to prevent the likelihood of a miss-selection, it also is a good idea to regularly update the outsourcing policy and strategy so that it is continuously in line with current management goals and objectives.

After investigations have been performed and the list of potential contract manufacturers has been narrowed down, the author strongly recommends that an on-site investigation of the contractor's facilities be made. Table B and Table C show examples of a comparison study conducted on three API and three pharmaceutical contract manufacturers. Each criteria should be assigned a value from 1~10, with 10 meaning top priority or most critical. For instance, if the timeframe, quality, and speed are regarded to be the most critical factors in the decision making process, 'Quality Standard' and 'Timeline for Implementation' should be given a '10.' Matrix type systems like the ones shown in the tables offer a very clear and objective approach to outsourcing decision making and lessen the selection risk. This type of system also can be used to evaluate in-house capacity and capability through self evaluation. In these case studies, there should be chosen Company A for API manufacturing site and Company Z for pharmaceutical manufacturing site respectively.

Contracting Process

After a decision has been made regarding which stages of the product lifecycle will be outsourced, formal contractual negotiations must take place with the selected contract manufacturer. Unlike moving forward with an in-house project, there can often be time consuming complications and/or difficulties agreeing on certain aspects of a contract. For this reason, it is very important to pay special attention to the project timeline and complete tasks as timely as possible. Figure 4 is an example of a typical project flow diagram from initial discussion through to the start of manufacturing. For early clinical manufacturing projects that do not require the purchasing of new equipment or facilities, it takes approximately three to six months from initial negotiations to production start. On the other hand, for commercial manufacturing projects that require installation of the new equipment or facility, process validation, regulatory submission, and approval, it takes approximately two to three years.

Contract Manufacturer Issues

The article thus far has primarily focused on the selection process of a contract manufacturer from an outsourcer's point of view; however, we will now look at this process from the contract manufacturer's point of view.

In the past, pharmaceutical companies have traditionally thought of contract manufacturers as 'Receivers.' In other words, a technology is transferred to the contractor and the contractor performs the tasks accordingly with very little input. Today, the outsourcing process is considerably more dynamic and contract manufacturers are often able to offer the outsourcer added value in terms of technology, quality and cost competency, and in many instances can offer value beyond methods and practices employed by the outsourcer. In reflection to this, contract manufacturers have earned the title 'Value-Creator' and a shift in the outsourcing paradigm has occurred. In realizing the benefits of contracting with a 'Value Creator,' outsourcers are aligning corporate cultures and becoming considerably more open to mutually beneficial relationships with the aim to create win-win situations.

Good business partnerships are initially formed at the start of the contracting process. It is a good practice for contract manufacturers to develop a contract agreement template so that this can be used as a basis for negotiations. If a contrac-

Continued on page 20.

Premium Design, without the Premium Price

USP Water Systems for Life Sciences

USPure Standard Water Treatment System

At Mar Cor, we focus on what we do best, providing high quality, microbiological controlled water purification systems for the pharmaceutical, beverage, cosmetic and other life science markets. Ask us to demonstrate why the USPure single skid system is the best value in high purity water.

Minncare Disinfectants

FiberFlo Filters

Water Treatment Systems

Support Services

MAR COR® PURIFICATION

A Cantel Medical Company

Competent, Consistent, Compliant

ISO 13485:2003 Certified • Mar Cor Purification • 800-633-3080 • www.mcpur.com

tor does not have a template, they are more likely to be in a weaker position during negotiation procedures and may end up adopting the outsourcer's standards despite the standards being inadequate or unfair.

Drafting contracts generally consumes a lot of time. In order to lessen the time it takes to draft and approve a contract, it is often a good idea to establish a business term sheet. The business term sheet should include, the price,

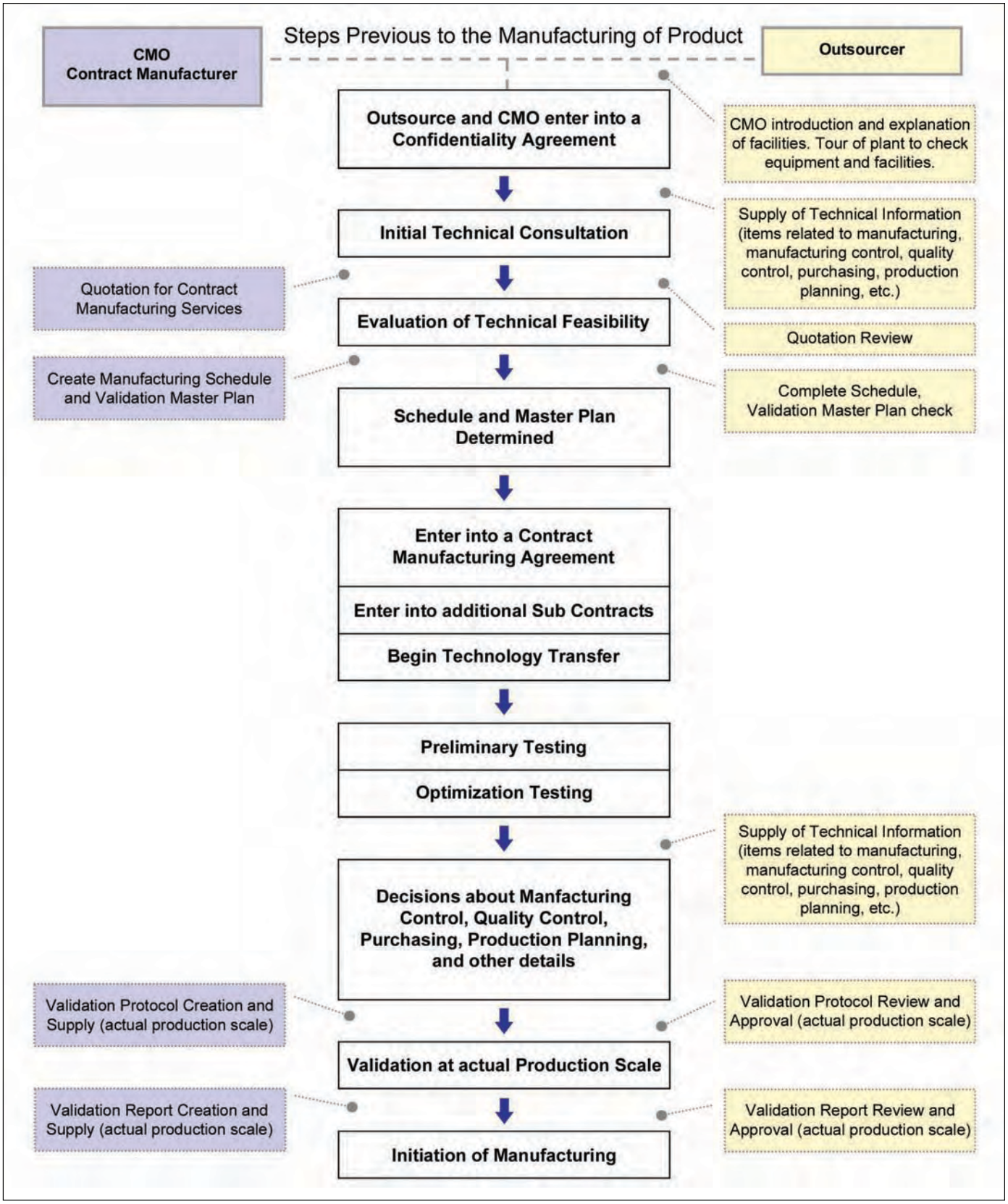


Figure 4. Typical contract manufacturing flow.

Continued on page 22.

ARE YOU RELYING ON SAFETY PRODUCTS THAT *"SHOULD"* WORK?

FIKE IS COMMITTED TO RELIABLE SAFETY SOLUTIONS THROUGH RESEARCH, NEW TECHNOLOGIES, AND EXTENSIVE TESTING.

EXPLOSION PROTECTION • PRESSURE RELIEF • TESTING SERVICES

- Comprehensive selection of ASME, CE and 3-A rupture/bursting discs
- High performance explosion vents, specifically designed for sanitary applications
- Complete line of products designed for CIP/SIP applications
- Dedicated team of combustion engineers and pressure relief experts

DON'T LEAVE THE SAFETY OF YOUR BUSINESS TO ANYTHING LESS THAN THE MOST RELIABLE, PROVEN PRODUCTS.

EXPLOSION VENTING

EXPLOSION SUPPRESSION

RUPTURE DISCS

FULL-SCALE TESTING

Fike®

WWW.FIKE.COM

PROVEN PERFORMANCE, QUALITY AND RELIABILITY FOR OVER 60 YEARS

1-866-758-6004

Visit us at Interphex Canada and the Chem Show

"The pharmaceutical industry has great opportunity for continuous growth. Within this industry, manufacturing also is expected to experience positive growth because there continues to be a need for innovation related to stable product supply, consistent quality, and cost competition."

price adjustments, required investments, manufacturing volumes, payment terms, contract length, and forecasting. Price adjustment clauses are possibly the most important. For contract manufacturers, it is extremely important to secure the absolute minimum amount of payment for services when manufacturing volumes are at their lowest due to unforeseen external environmental factors. At the same time, cost pricing for the different volume sizes in addition to the negotiation of a minimum volume also should be established. Other areas that also are important to include are clauses related to facility cost sharing, insurance fees in the case of lot failures or unforeseen disasters, and intellectual property.

It is now common practice to negotiate a quality agreement in addition to the contract manufacturing agreement. The quality agreement normally includes specific details related to the quality of the product, the term of the quality agreement, and the notification system of who to contact when certain circumstances arise. Other areas covered are GMP compliance issues, maintenance of testing methods and specifications, the right to audit the contract manufacturer's facility's, procedures to follow if notification from a regulatory authority is received and clauses related to third party contracting, change control and validation, deviation and Out of Specification (OOS) notification, annual product review, documentation storage, stability testing, reference sample storage, and complaint/recalls. While it is important for contract manufacturers to establish their own quality agreement template, many of the requests being made will be a result of the pharmaceutical company's corporate policies. Again, having your own agreement will help during the negotiation process.

Conclusion

The pharmaceutical industry has great opportunity for continuous growth. Within this industry, manufacturing also is expected to experience positive growth because there continues to be a need for innovation related to stable product supply, consistent quality, and cost competition.

The CMC function also is an extremely important role within companies because this is where new potential products are discovered and nurtured, ultimately leading to the generation of profit for the developing company and the industry as a whole. At the development stage, CMC not only covers clinical supply, but also many critical development areas that lead to the final goal of product launch.

The current philosophy of the pharmaceutical industry is that in these times of economic difficulties and hardships, it is not considered a reasonable approach for all manufacturing and development activities to be performed in-house. There are too many benefits related to cost, human resource, material management, and speed to competitively conduct all development activities in-house. A strategic approach to outsourcing is required for all stages of the product lifecycle and a clear selection guideline should be established.

For contract manufacturers, on the other hand, quality, cost competition, and the ability to offer a stable and on-time product supply will continue to be key. The adoption of additional 'value added' competencies like "Kaizen" or "Continuous Improvement" in terms of both cost and quality also will become important areas for contract manufacturers to focus on in the future.

There is absolutely no doubt that contract manufacturing will continue to become an increasingly significant part of the pharmaceutical industry during all stages of the product lifecycle. The future will see an increasing level of strategic partnerships and alliances between pharmaceutical companies and contract manufacturers with the ultimate goal of creating mutually beneficial relationships.

References

1. IMS Health News Releases, "IMS Health Lowers 2009 Global Pharmaceutical Market Forecast to 2.5-3.5 Percent Growth," 22 April 2009.
2. IMS Health News Releases, "IMS Health Forecasts 4.5-5.5 Percent Growth for Global Pharmaceutical Market in 2009, Exceeding $820 Billion," 29 October 2008.
3. PricewaterhouseCoopers Japan, Pharma 2020: Vision, pp 2-3.
4. Indian Business Journal, 14 June 2007.
5. Business Insights "Contract Manufacturing Strategy: Market Developments, Technology Transfer and Key Success Factor," May 2008. http://www.chidb.com/Business_Insight/descriptions/contact_manufacturing.asp
6. Jayakumar, P .B., "Global Pharmas Prefer Emerging Drug Makers Over Indian Giggies," 8 January 2008. http://www.rediff.com///money/2008/jan/08pharma.htm.
7. Business Insights, "Pharmaceutical Outsourcing Series, Contract Manufacturing," http://www.globalbusinessinsights.com/pharmaceutical_outsourcing/pharma_outsourcing_CMO.htm
8. Akio S., "Seisakuken News," *Office of Pharmaceutical Industry Research,* Vol. 26, 2008, pp 32.
9. Hussain M., Fenella S., "Contract Manufacturing Competition," *Contract Pharma,* March 2008.
10. Swati C., "Outsourcing in Pharmaceutical Industry," Bionity.com Articles. http://www.bionity.com/articles/e/49803/
11. PhRMA "Pharmaceutical Industry Profile 2009."

About the Author

Takayuki Kasai is the President of Bushu Pharmaceutical Ltd. in Japan. He graduated from Tokushima University and received an MS in organic synthesis for hetero-cycle compounds. He has a wealth of experience in the pharmaceutical analysis and manufacturing areas, including analytical research, physicochemical property, stability, degradation path, and establishment of specifications and test methods for new drugs, DMF/NDA preparation, chemical process development/improvement, and CMC project management. He was head of clinical manufacturing during his 20 years at Shionogi & Co., Ltd. Also during his time with Shionogi, he trained at Schering-Plough in the US for two years. He was an original member of Japanese PDA API Committee established in 2001 until his appointment of President at Bushu Pharmaceuticals. He is currently the Chairman of the Saitama Prefectural Pharmaceutical Association. He can be contacted by telephone: +81-49-233-4651 or by email: takayuki.kasai@bushu-seiyaku.co.jp.

Bushu Pharmaceuticals Ltd., 1 Takeno, Kawagoe, Saitama, 350-0801, Japan.

This article discusses the nature of organizational change with respect to offshore outsourcing of IT activities in the different Information Systems Departments (ISDs) of a global pharmaceutical company and examines the effectiveness of approaches used to manage this change.

Change Management during Offshore Outsourcing: Success Factors for Implementation

by Dr. T.R. Ramanathan

Introduction

The business environment for large pharmaceutical companies has changed considerably in recent years. The cost of developing a new drug (Figure 1) has risen nearly four times to $1.3 billion since 1987[1] and pharmaceutical companies are now spending an average of 17 percent of sales (Figure 2) or about $3 billion per year on R&D activities. At the same time, pharmaceutical companies also are witnessing an industry-wide decline in R&D productivity - *Figure 3*. These pressures are prompting an increasing number of pharmaceutical companies to undertake various change initiatives ranging from mergers and acquisitions and partnering with biotechnology firms to strategically outsourcing a number of activities across the value chain, including support functions such as Information Technology (IT), human resources, and finance to control costs and improve revenues by reducing the time-to-market of new drugs.

As pharmaceutical companies seek ways to boost the efficiency of their processes and streamline complex internal operations, their interest in using offshore outsourcing to meet these objectives has grown significantly in recent years. For example, AstraZeneca signed a multi-million dollar, five-year outsourcing agreement with the Indian IT firm Infosys in December 2008, which provides end-to-end IT application maintenance services to the company's global operations in areas such as manufacturing, supply chain, finance, human resources, and other corporate functions. Similarly, Bristol-Myers Squibb announced in September 2008 that it had signed a new 10 year, $550 million contract with Accenture for providing a range of finance and accounting and IT application development and maintenance services, thereby extending the scope and duration of an existing four year outsourcing agreement. Although the industry's interest in offshore outsourcing originally stems from lower labor costs for IT services, many pharmaceutical companies are now rapidly moving to capture gains beyond labor cost savings in back-office operations.[2] With the recognition of offshore outsourcing as a key business strategy by more and more companies, there is less emphasis on cost reduction and more emphasis on flexibility and speed required to meet changing business needs, access to new technologies and expertise, productivity gains, quality improvements, and revenue growth.

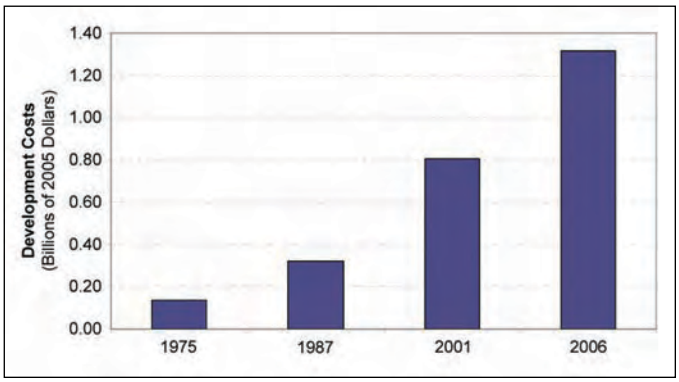
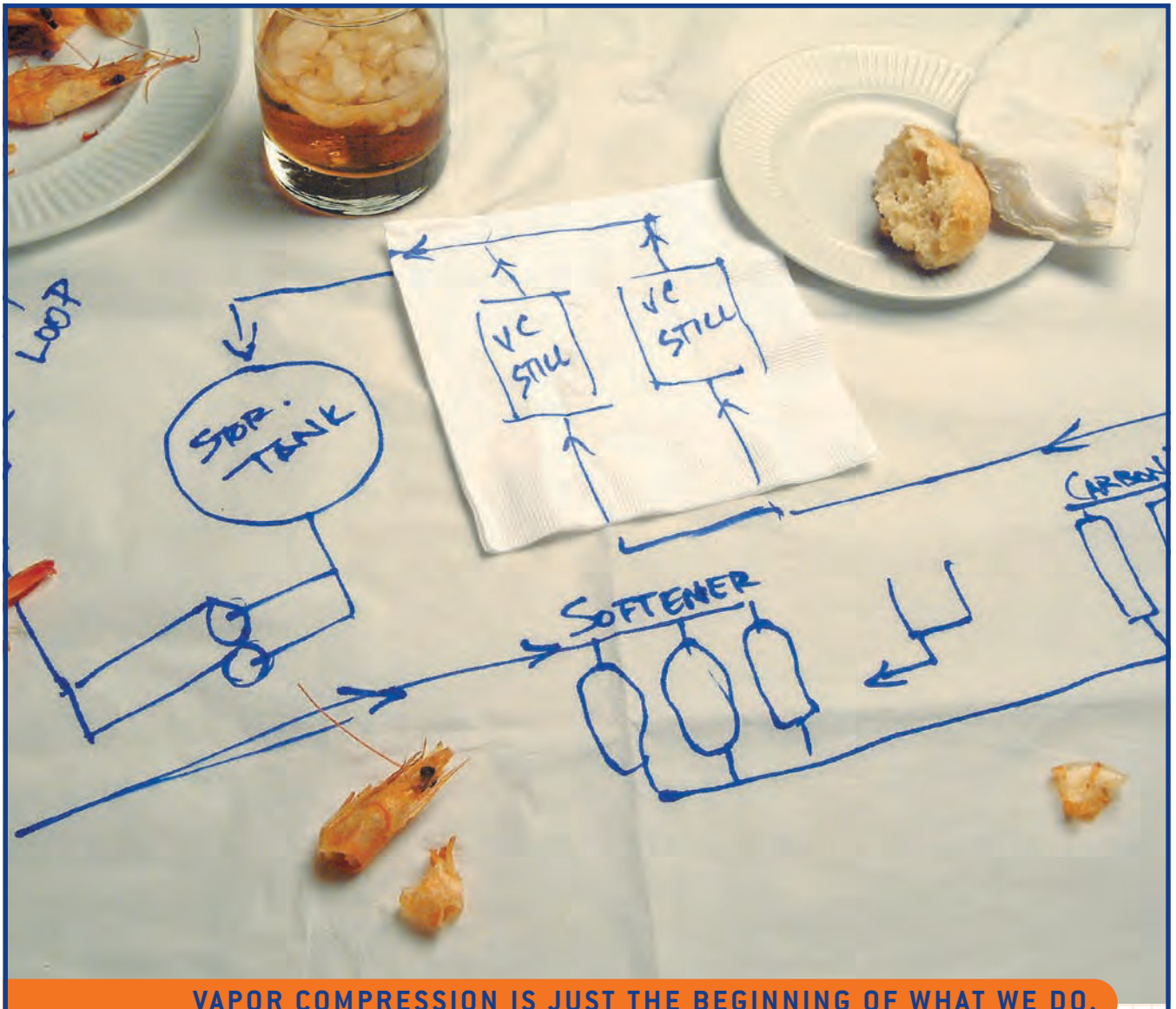


Figure 1. Growth in drug development costs – 1975 to 2006. (Source: Pharmaceutical Research and Manufacturers of America (2008))

While some experts have suggested that the overall demand for offshore outsourcing has reduced in the wake of the current global economic slowdown, the impact of the economic downturn on offshore outsourcing appears to be of lesser significance in the pharmaceutical industry than in other industries. The reason is because, even prior to the onset of the economic downturn,

Continued on page 26.



VAPOR COMPRESSION IS JUST THE BEGINNING OF WHAT WE DO.

Innovative Solutions For Purified And WFI-Grade Water And Pure Steam.

It was a big idea that simply got bigger. Today, MECO has grown to provide expert guidance and customized solutions for every phase of water and Pure Steam generation. Whether you need a particular product, a specialized service or an entire water plant designed and built from scratch, MECO delivers. To see for yourself, visit mecobiopharm.com or call 1-800-421-1798.

MECO

MECO NO BOUNDARIES PROMISE

PEOPLE | PRODUCTS | SERVICE

US _ UK _ Singapore _ UAE _ 800-421-1798 _ mecobiopharm.com

12505 Reed Road, Suite 100, Sugar Land, TX 77478

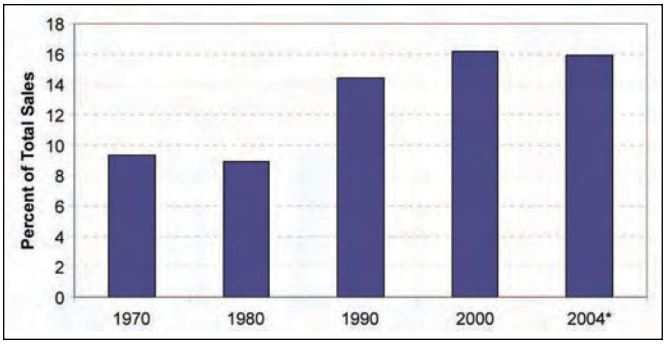


Figure 2. Pharmaceutical industry R&D expenditures as a percentage of total sales – 1970 to 2004. (Source: Pharmaceutical Research and Manufacturers of America (2005))

pharmaceutical companies had recognized the need to reduce their ratio of Selling, General and Administrative (SG&A) expenses to net sales, and had already begun to outsource support functions and indirect procurement in order to reduce their overhead costs. In addition to having relatively strong interests in reducing the cost of support functions, their focus for cost reduction lies in removing cost from major industry-specific processes, such as warehousing and logistics, customer account administration, adverse events processing, litigation case processing, and patent related issues.[3]

With pharmaceutical companies turning to offshore outsourcing to achieve cost efficiencies and shorten product lifecycles, many offshore initiatives are failing to meet performance expectations because offshoring causes far-reaching changes throughout the organization, which are often poorly managed. Despite the proliferation of models and best practices to aid the successful diagnosis and implementation of change efforts, two out of every three change initiatives fail, according to a recent global survey of 3,199 executives by McKinsey & Company.[4, 5] The survey revealed that managers immerse themselves in an "alphabet soup of initiatives" without fully understanding the nature and process of corporate change. As a result, there is a growing need for organizations to understand how change related to offshore outsourcing occurs so that they can manage this change process more effectively.

Against that background, the author's research study aimed to understand: 1) the nature of organizational change with respect to offshore outsourcing of IT activities in the different Information Systems Departments (ISD) of PharmaCom (pseudonym) and 2) to examine the effectiveness of approaches used to manage this change so that lessons may be drawn from these experiences. The research employed a qualitative case study approach to gain an in-depth understanding of the processes, organizational factors, and effects of change related to offshore outsourcing in three ISDs of the company (i.e., R&D, Sales and Marketing, and Corporate Information Systems Group). These ISDs served as the units of analysis for the investigation, and an analysis of similarities and differences of the offshore program outcomes across these ISDs provided the basis for drawing conclusions. The author hopes that policy makers and change managers will be able to use the results of the study as well as the recommendations to enhance the planning and implementation of future offshore outsourcing initiatives in order to achieve positive organizational outcomes.

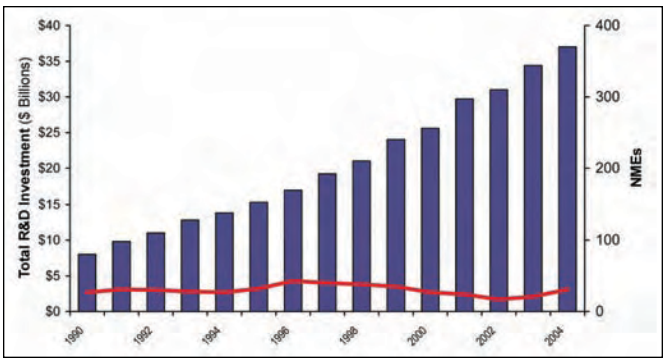


Figure 3. Pharmaceutical industry productivity vs. R&D investment. (Source: Pharmaceutical Research and Manufacturers of America (2000, 2008))

Case Study

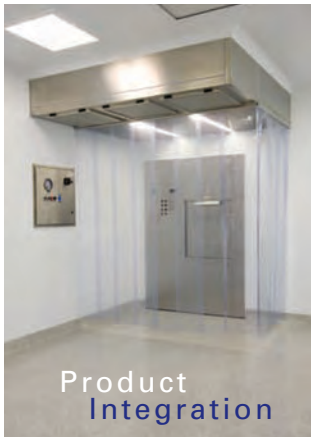
PharmaCom, a global pharmaceutical company with access to worldwide resources and markets, is not insulated from any of the forces impacting the pharmaceutical industry that were previously described. In order to address these challenges, PharmaCom undertook a detailed review of its strategy and concluded that its current structures and processes, developed over many years, were too complex and no longer conducive to sustaining strong business performance. It also was concluded that PharamCom needed to respond to the changes in the business environment being observed in many of its markets, in particular increased governmental restrictions imposed on healthcare spending and impending patent challenges to two of the company's top-selling drugs.

In 2003, PharmaCom's top executives decided to launch a set of company-wide reshaping initiatives aimed at improving the quality of its processes and business, focusing on value-adding activities, eliminating inefficiencies, and freeing resources so that the company could invest more in future growth. These change initiatives were intended, in the long term, to improve resource allocation and to increase the quality of PharmaCom's business by creating the level of excellence needed to implement its business strategies, while continuing to generate sustainable growth in a more challenging environment. The management projected that, in just less than three years, $625 million a year could be reallocated on a permanent basis as a result of these initiatives. The projected financial savings were seen as validation that the new initiatives ensured the company's future in terms of new products, while protecting its earnings growth.

Executive management took a business function-based approach to implementing the reshaping initiatives. A range of individual initiatives were proposed in several geographical regions and in the Sales and Marketing, Research and Development, Manufacturing, and Finance and Administration Business Functions. As an example, in Finance and Administration, the management initiated several projects to improve quality and overall productivity and efficiency, including one

Continued on page 28.

A Single Resource...



for TOTAL Cleanroom Confidence.

Planning & executing the right cleanroom solution for your critical process.

AES is your single resource to deliver fast track solutions for Pharma & BIO applications, such as:

- **API Clean Containment**
- **Fill/Finish Processes**
- **Blow/Fill/Seal Facilities**
- **EU/Grade A Laminar Flow Upgrades**
- **Low cost ISO 8/CNC Macro Environments**
- **Cell Manufacturing Facilities**

With the AES Pharma Wall System, combined with our expert knowledge of HVAC and process integration, let us show you how the AES "single resource" team can deliver maximum value to your cleanroom investment.

Call Grant Merrill at 888-237-2532 (ext. 139) to arrange your free consultation today.

aes
Clean Technology, Inc.

1-888-AES-CLEAN ext. 139
237-2532

aesclean.com

focused on implementing an offshore outsourcing strategy for IT projects and services. The Sales and Marketing ISD had already experienced success with offshore outsourcing on IT projects (on a smaller scale) suggesting that this approach was worth exploration on a larger scale at the enterprise level.

The management proceeded with caution, redirecting only a portion of the total external IT spending to offshore companies. The rationale was that the company could first test the long-term feasibility of the offshore IT outsourcing strategy, while being sensitive to and mitigating initial fears and concerns of employees by demonstrating management's ability to manage offshore outsourcing without negatively impacting internal staff. The offshore IT outsourcing initiative was led by a Change Management Team (CMT) comprising of senior staff members from the different ISDs. The CMT was charged with planning and implementing the offshore initiative within the different ISDs, taking into account its potential impact on the company's business and on the ISDs' human resources. With the CMT in place, the executive leadership had created the organizational structure and conditions necessary for the adoption of offshore IT outsourcing in the company.

During the latter part of 2003, the CMT organized workshops to examine lessons learned from the previous offshore IT outsourcing experience. The CMT members also received a full day of education from both internal experts and external agencies (such as Gartner and Infosys) in order to help them overcome their initial fear of offshore outsourcing. More specifically, the workshops examined offshore trends in application software outsourcing, potential benefits and drawbacks of the different offshore delivery models (i.e., onsite, onshore, nearshore and offshore – see Table A for a list of pros and cons of these approaches), myths and realities regarding cost savings, factors to consider in supplier selection, and critical success factors. These workshops also reviewed several case studies from various industry sectors in application software outsourcing, focusing on business challenges that were driving outsourcing decisions, the scope

Delivery Mode	Benefits	Risks	Outsourcing Strategy
IN-HOUSE DEVELOPMENT			
	• Security • Business Continuity • Intellectual Property Protection • Infrastructure	• High Labor Costs • Availability of Relevant Skills • Low Efficiency • Management Burden	
CAPTIVE CENTERS			
Offshore/Nearshore	• Security • Business Continuity • Intellectual Property Protection • Infrastructure • Low Labor Costs • Availability of Relevant Skills • Service Quality • Size and Quality of Labor Pool	• High Management Effort • Financial Risk (i.e. initial investment) • Start-up Costs: - Infrastructure - Hardware - Software	
GLOBAL DELIVERY MODEL			
Onsite	• Proximity to Client • Security • Business Continuity • Intellectual Property Protection • Infrastructure • Cultural Fit	• High Labor Costs • Availability of Relevant Skills	Typically staff augmentation
Onshore	• Proximity Limited to On-demand Presence at Client Site • Business Continuity • Infrastructure • Project Management Capabilities • Business Process Expertise • Fixed Cost • Cultural Fit	• Security • Intellectual Property Protection • High Costs • Hidden Costs (Travel, Communication) • Scope Changes can Escalate Costs	Project-based consulting and system integration
Nearshore	• Same Time Zone • Relatively Lower Costs • Infrastructure • Language Skills • Shared Business Culture	• Security • Intellectual Property Protection • Business Continuity • Hidden Costs (Travel, Communication) • Scope Changes can Escalate Costs	Project-based consulting and system integration, and Service outsourcing (infrastructure or business processes)
Offshore	• Low Cost • Availability of Relevant Skill Sets • Process and Methodology (Certifications) Maturity • Service Quality • Size and Quality of Labor Pool	• No Proximity to Client • Time Zone Difference • Communication/Language Issues • Security • Intellectual Property Protection • Scope Changes can Escalate Costs	Staff augmentation, project-based consulting and system integration, and Service outsourcing (infrastructure or business processes)

Table A. Pros and Cons of the major IT sourcing approaches.

Continued on page 30.

Filling x Freeze Drying x Loading / Unloading

=Experience^3

Next generation of **aseptic vial processing**

4-lane **time-pressure** dosing system **100% IPC**

Freeze dried or conventional processing of the most **diversified substances**

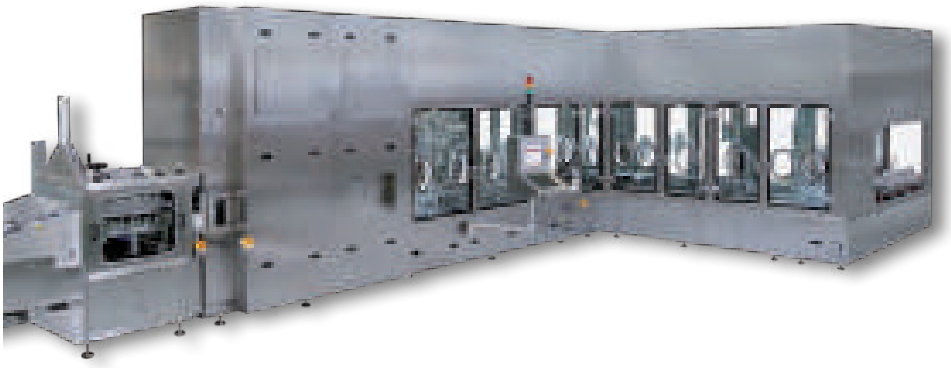
Automatic loading and unloading **freeze-drying**

Isolator design for **maximum protection**

OPTIMA GROUP

pharma

INOVA
KUGLER
KLEE



get more information on www.vial-filling.com

OPTIMA GROUP pharma GmbH, 74523 Schwäbisch Hall, Germany, Facility 35075 Gladenbach, Germany
OPTIMA Machinery Corporation, 1330 Contract Drive, Green Bay, USA

Member of

PACKAGING VALLEY Germany

of services covered by application outsourcing engagements, key factors and attributes involved in vendor selection, and criteria for measuring success.

As part of data gathering and analysis, the CMT evaluated the following risks associated with IT offshoring and identified strategies for mitigating them: threats to intellectual property; loss of control over the outsourced activity; customer dissatisfaction; impact of poor service quality; and loss of data security, business continuity, and IT skills and expertise. The CMT decided not to offshore any core IT activities, including the development or maintenance of any regulated IT systems (such as submissions, clinical trials, labelling, drug safety, etc), as outsourcing these could expose the company to unexpected risks. In early 2004, the CMT required each ISD to offshore at least one IT project or service, following the CMT's guidelines and criteria for offshoring. As a result, a total of 24 projects/services were identified from the different ISDs for offshore implementation during the first year of operation. For example, in the Sales and Marketing ISD alone, 15 projects were identified for potential offshore implementation with a number of them to be delivered on a fixed-price basis, thus representing significant savings for the ISD. To illustrate, this ISD expected to save at least $1.25 million per year from just two of these 15 projects. Similarly, the R&D ISD sought to establish an Offshore Development Center (ODC) in India, providing expertise in four critical software technologies (i.e., Documentum, Plumtree Portal, Tibco, and Informatica). The ODC, with 13 full-time personnel, was to provide software development and maintenance services in these technology areas, and represented a total annual savings of more than $500,000 for the R&D ISD.

With regard to vendor selection and sourcing, the CMT initially examined 16 vendors and selected six for more intensive screening. This process included field visits to vendor facilities in India to meet their staff and to understand their processes and capabilities. The assessment (see Table B for vendor evaluation criteria) focused on the ability of the vendors to adapt or tailor their work processes to meet PharmaCom's needs. The CMT finally selected three vendors, to which the ISDs could outsource their projects or services. A two-year outsourcing agreement was negotiated and executed with each of these vendors, providing default contractual obligations between PharmaCom and the vendors. The outsourcing agreement required each work assignment to execute a Statement of Work (SOW) with an associated Service Level Agreement (SLA) and cost schedule. The ISDs were required to follow a Request for Proposal (RFP) process for each project or service execution to competitively select a vendor from among the approved vendors.

Evaluation Area	Criteria
Company:	Vision and direction Company stability (finance, customer base) Size Location: onshore/nearshore/offshore Security Organizational culture
Technology:	Project management Software development process Quality process
Human Resources:	Skill sets People quality Retention rate Training and development

Table B. Vendor evaluation criteria.

The ISDs had considerable freedom to design and implement the necessary governance structures and organization to manage these offshored projects/services within the overall offshoring framework put in place by the CMT - *Figure 4*. The ISDs created their own Project Management Offices (PMOs) to oversee operations, handle vendor management, enforce compliance with quality requirements, and track and report performance.

Key Findings

The findings from the study suggest that a confluence of external and internal contextual pressures for change created an environment receptive to the adoption and use of offshore outsourcing at PharmaCom. The external context, particularly the economic forces, was found to be primary catalyst promoting change initiatives, such as offshore outsourcing in cost-oriented organizations. However, recent research indicates that the strength of cost pressures can vary by the sector and can depend on the competitive intensity of the sector.[6] Based on the data, it appears that the R&D productivity crisis is a necessary condition for companies in the pharmaceutical industry to adopt strategies, such as offshore outsourcing, to reduce drug development costs and to improve R&D productivity. Regulatory concerns remain an important challenge to the adoption of offshore outsourcing, reinforcing the findings of previous research by Farrel, Laboissiere, and Rosenfeld (2006). New technologies have become a significant source of competitive advantage in the pharmaceutical industry by accelerating drug discovery and development, supporting the notion that businesses have come to increasingly rely on IT to achieve and maintain sustainable competitive advantage.[7] Investment in information technologies, in particular, increase business efficiencies, while offshore outsourcing of IT services is instrumental in deriving maximum value from these investments.

Within the context of a changing external environment, the internal context further explains the rationale for the adoption of offshore outsourcing at PharmaCom. The role of the executive leadership was central to this adoption. Examination of the organization's internal (and external) environment by the top leadership appears to have led to the introduction of strategies aimed at gaining competitive advantage. Resource consideration, notably the lack of human and financial resources, was a dominant factor influencing the adoption and use of offshore outsourcing within PharmaCom. The shortage of internal IT staff to satisfy the growing demand for IT services, coupled with budget constraints, provide an important incentive to support the adoption of offshore outsourcing. Lack of internal resources was identified as a dominant factor in all three cases, validating the suggestion by previous

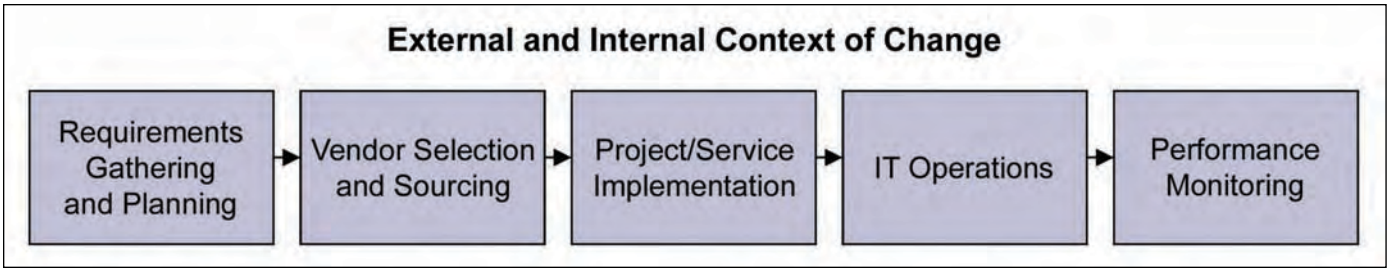


Figure 4. High level offshore outsourcing process.

research that it is the "scarcity of local talent that prompted companies in the US and Germany to hire offshore at the end of the last decade."[6] A proper understanding of the organization's internal environment (e.g., resource constraints) is necessary for leaders so that they can take into consideration these internal variables while planning a change initiative. This aspect is noteworthy in this study since in much of the change literature the focus is on external factors.

The findings also suggest that several organizational factors in combination are necessary for the successful diagnosis and planning of change with respect to offshore outsourcing in IT organizations. For example, the study found that factors, including data gathering and analysis, a solid change management team, adequate resource allocation, feedback mechanisms, and performance measurement contributed to the successful management of change. On the other hand, factors such as the lack of a sense of urgency, the lack of a vision, the failure to clearly identify the benefits of the change, lack of education and training in cross-cultural communication, and poorly designed vendor selection process were found to hinder successful change management.

With the implementation of change, the study found that various organizational factors, including management of transition to the new state, pilot projects to facilitate the assimilation of change, and proper management of day-to-day operations contribute to successful offshore outsourcing implementation. At the same time, failure to effectively communicate the vision, the directive (top-down) implementation approach, the lack of strategies to manage employee resistance, and the lack of plans to develop a fit between the change and the organizational culture were perceived as significant barriers to offshore outsourcing implementation.

Continued on page 32.

In terms of the effects of change, the study found that the main effects of the offshore initiative include performance of multiple roles by employees in change implementation and management expectations of these roles, as well as benefits of collective learning that help to take corrective actions to achieve the desired future state. Also, rewards are particularly viewed as critical for adopting new behaviors related to the change. Demonstration of positive results during the course of the change process and ensuring leadership support is linked with helping to institutionalize the change.

In sum, the successful introduction of offshore outsourcing within an IT organization and the smooth transition to the desired future state depends on the change strategy adequately addressing all of the abovementioned organizational factors. Taking these factors into account during the planning phase helps to minimize employee resistance to change and contributes to successful outcomes. In addition, senior management must make every effort to maintain high employee morale during offshore outsourcing, including treating employees appropriately by providing adequate support and reasonable remuneration deals.[8]

Implications for Change Management Practice

The issues raised in this study have implications for both policy makers as well as change managers. Many of the recommendations set out below have already been well attested by the change management experiences of organizations in other industries.

Recommendations for Policy Makers

Building Commitment to Change

Building commitment starts with communication from the executive leadership explaining the need for change. The communication must aim to sensitize employees and other stakeholders to the contextual factors, both internal and external, that have led to the consideration of the change. The employees and other stakeholders must understand why the organization is embracing offshore outsourcing and how this change will affect them. When they understand that offshore outsourcing is driven by legitimate business drivers, they are more likely to accept it. Without a clear understanding of these business drivers, they may come to view the change as unjustified and burdensome, thus increasing the likelihood of resistance to offshore outsourcing initiatives.

Aligning Outsourcing Objectives with the Corporate Vision

Successful offshore outsourcing depends on having a clear corporate vision that aligns offshore outsourcing with business objectives and a demonstration of conviction by executives that offshore outsourcing will help in realizing the corporate vision. Aligning the outsourcing strategy with business objectives can provide several potential benefits to a business, including more competitively priced products and services, greater return-on-investment, increased profit margins, growth, etc. However, aligning outsourcing objectives with the corporate vision does not itself guarantee that workers will embrace offshore outsourcing, especially if jobs will be displaced due to offshoring. Employees are less likely to resist the change when they see offshore outsourcing as improving the long-term viability of the company through increased profits and business growth. On the other hand, if they determine that offshore outsourcing is being pursued only to meet short-term cost reduction goals, including layoffs, they may resist the change.

Change Management Team

It is imperative for top-level executives to recognize that having an effective change management team (or change agents) is a critical success factor in implementing offshore outsourcing programs. This team must be powerful in terms of titles, information, expertise, reputations, and relationships[9] to be able to remove obstacles to the change and deliver on the change outcomes. More importantly, the individual team members must possess credibility as leaders and be free of self-interest and hidden agendas so that they can win the trust of the employees and other stakeholders. Also, the change management team's membership must be representative of the different departments and units impacted by offshore outsourcing, and individual team members will require change management competence to deliver the results for which they are accountable.

Executive Sponsorship

Top executives can play a crucial role in successful change management by actively participating throughout the change management process. Through the sponsorship of specific projects or initiatives, these executives can not only demonstrate their commitment to the change, but also can show that the proposed change aligns with the business objectives. Getting the projects or initiatives incorporated into the sponsors' objectives gives them the incentive to make change work.[10]

Recommendations for Change Managers

Vision for Change

Offshore outsourcing, as with any major change, requires the development of a clear vision that describes a "big picture" of the desired future state. The commitment of the change managers (assuming that the change managers are responsible for initiating the change) must flow from the clarity of the vision and it must percolate down the organization creating buy-in at all levels. A good vision is imaginable, desirable, feasible, focused, flexible, and communicable.[9] Finally, the change managers must translate the change vision to the external service providers in terms of change implementation strategy and performance goals and measures, which must be clearly understood and agreed upon by the service providers.

Communicating the Vision for Change

The importance of communicating a vision during a significant change effort, such as offshore outsourcing, cannot be overstated. Change management experts state that a vision-driven change requires extensive and creative use of communication

strategies.[11] In communicating the vision, the change managers not only establish credibility with employees, but also help to minimize employee resistance to the change.

Sense of Urgency

Change mangers can set the stage for offshore outsourcing by instilling a sense of urgency within the organization. A "burning platform" is essential to alert and motivate the organizational members to the need for change and gain their cooperation to bring about the change.[9]

Communication Plan

A vital element in motivating people to change is the effective communication between the change managers and the stakeholders impacted by the change. Lack of and insufficient communication is one of the main reasons why change efforts fail. Change management experts note that selecting the appropriate method for communication, as well as deciding on the content of the communication, are extremely important.[12] In addition to using a formal communication plan to communicate, change managers must engage the different stakeholders in an open dialogue about the change and allow them to state their views and to provide feedback into the change process. Frequent communications are important during the planning and implementation stages, as this helps to alleviate employee fears and begins to build support for the change. Change managers can utilize existing and regular forms of communication, such as newsletters, web sites, meetings, etc to get the message out.

Change Implementation Strategy

A change strategy is a critical component of any offshore outsourcing initiative. To develop an effective strategy, change managers must determine the long term goals and objectives of the offshore outsourcing effort. By encouraging the involvement of the middle management and non-managerial level employees in this strategy development process, their buy-in can be created from the very start.

Teamwork

In order to create buy-in from the employees early in the change process, the change management team should consider creating and leading cross-functional working groups, comprised of middle management and non-management level employees, to work on aspects of design and planning (tasks could include data gathering and analysis, developing new work processes, developing performance measures, etc.). In so doing, the change managers empower these groups to act on the change and signal to them that their input is considered important, thereby reducing resistance to the change.

Education and Training

A key element of change management is the identification of the education and training needs of the organization with a view to develop new competencies (knowledge, skills, and attitudes) for managing the transition to the desired state. To better manage offshore initiatives, change managers can develop a training curriculum for employees who will be retrained in the new competencies and the training should include topics, such as vendor relationship management, cross-cultural communication, contract management, vendor performance monitoring, and conflict management.

Pilot Projects

Change managers must consider introducing large scale changes, such as offshore outsourcing, gradually through small projects. Pilot projects provide the opportunity to test one or more of the alternative approaches to offshore outsourcing, thus offering valuable lessons for further implementation. Moreover, they are less risky and successful pilot projects can stimulate interest in larger-scale projects. Change managers should highly publicize and even reward success from pilot projects in order to reinforce new behaviors.[7]

Performance Monitoring

Setting up clear measures of performance is vital to the process of managing change. The performance measures should focus on reviewing the effects of the change through systematic information gathering and analysis. A good monitoring system combines elements of both quantitative and qualitative measures to produce timely information about progress toward stated goals and can help detect potential problems before they arrive.

Concludes on page 34.

Job Roles and Organizational Design

As an organization considers offshore outsourcing, change managers must identify affected roles and develop new roles and organizational structures for ensuring ongoing management and oversight of offshored activities. It is important to clearly define and communicate the new roles and integrate them into the organization's performance management system. It is equally important to distinguish the roles and responsibilities between internal and offshore staff. In many cases, the role of the internal staff may be enhanced by shifting their focus to business issues, user interactions, and vendor relationship management.

Rewards and Recognition

One way to promote offshore outsourcing is by aligning the rewards and recognition programs to the new behaviors needed to institutionalize the change. Change experts state that by aligning the rewards and recognition structure, senior management can exhibit strong visible signs that the organization actually values what it claims to value.[13] The change management team can formally recognize individuals and teams in a public manner for their contributions and for demonstrating new behaviors. In addition, extrinsic rewards, such as cash, gifts, and pay increases, can be provided to acknowledge desired new behaviors. For those who are intrinsically motivated, intrinsic rewards should be implemented to further increase their participation.

Continuous Improvement

Change managers can play an important role in supporting a continuous improvement culture following a change. A continual improvement mindset can enable organizations to look for new ways to improve their offshored business processes through small incremental changes, thus generating improvements in efficiency and overall organizational performance.

Conclusion

With the growing globalization of the world economy, an increasing number of firms are using offshore outsourcing as a strategic tool to deal with cost pressures and rapidly changing market conditions. However, adapting to changes related to offshore outsourcing has been complex and challenging for firms to achieve due to various barriers, including differences in language and style of communication, working methods, organizational culture, and internal employee resistance to change. Overcoming these obstacles and capturing the benefits of offshore outsourcing requires firms to undertake well planned and executed change management programs. While ineffective change management can negatively impact a firm's competitive advantage in the market place, effective change management can positively impact the firm's profitability and shareholder value.

References

1. PhRMA, Pharmaceutical Industry Profile 2008, Washington, D.C.: Pharmaceutical Research and Manufacturers of America, 2008.
2. Bloch, M., Dhankhar, A., and Narayanan, S., "Pharma Leaps Offshore," *The McKinsey Quarterly,* July, 2006.
3. NelsonHall, BPO Opportunities in Healthcare and Pharmaceuticals Sector in 2009, Bracknell, United Kingdom: NelsonHall, p. 79.
4. Aiken, C. and Keller, S., "The Irrational Side of Change Management," *The McKinsey Quarterly,* April, 2009.
5. Beer, M. and Nohria, N., "Cracking the Code of Change," *Harvard Business Review,* May-June, 2000, pp. 133-141.
6. Farrell, D., Laboissiere, M.A., and Rosenfeld, J., "Sizing the Emerging Global Labor Market: Rational Behavior from Both Companies and Countries Can Help it Work More Efficiently," *The Academy of Management Perspectives,* Vol. 20, No. 4, 2006, pp. 23-34.
7. McNish, M., "Guidelines for Managing Change: A Study of Their Effects on the Implementation of New Information Technology Projects in Organizations," *Journal of Change Management,* Vol. 2, No. 3, 2002, pp. 201-211.
8. Khong, K.W., "The Perceived Impact of Successful Outsourcing on Customer Service Management," *Supply Chain Management: An International Journal,* Vol. 10, No. 5, 2005, pp. 402-411.
9. Kotter, J., **Leading Change,** 1st Ed., Cambridge, Massachusetts: Harvard Business School Press, 1996, p. 187.
10. Dobson, D., "Big Change Programs: Increasing the Likelihood of Success," *Journal of Change Management,* Vol. 2, No. 1, 2001, pp. 7-22.
11. Pitt, L., Murgolo-Poore, M., and Dix, S., "Changing Change Management: The Intranet as Catalyst," *Journal of Change Management,* Vol. 2, No. 2, 2001, pp. 106-114.
12. Goodman, J. and Truss, C., "The Medium and the Message: Communicating Effectively During a Major Change Initiative," *Journal of Change Management,* Vol. 4, No. 3, 2004, pp. 217-228.
13. Higgs, M. and Rowland, D., "Developing Change Leaders: Assessing the Impact of a Development Program," *Journal of Change Management,* Vol. 2, No. 1, 2001, pp. 47-64.

About the Author

T.R. Ramanathan holds a doctorate in business administration (DBA) from the Newcastle Business School at Northumbria University, United Kingdom. He obtained his MS and M.Phil. degrees in organizational dynamics from the University of Pennsylvania in Philadelphia. His research interests include organizational change, global sourcing, and IT portfolio management. He has worked for the pharmaceutical industry for more than eight years and was recently involved in managing offshore outsourcing operations for a global pharmaceutical company. He can be contacted by telephone: +1-609-433-9161 or by email: ramanathan_tr@yahoo.com

Newcastle Business School, Northumbria University, City Campus East, Newcastle-upon-Tyne NE1 8ST, United Kingdom.

Reducing the Cost of Compliance
With Risk-Based Testing of Your Balances

Adopt Good Weighing Practice™ (GWP®) into your quality management system to control your balances with minimal effort. GWP® provides all relevant testing procedures in a single document devised for auditing purposes.

- **Request your GWP® recommendation document**
- **Register for a GWP® webinar**
- **Check your weighing risk online**

www.mt.com/GWP

METTLER TOLEDO

This article discusses how to apply the GAMP 5 quality risk management strategy to maintain compliance in laboratory computerized systems.

Applied Quality Risk Management: Case Study – Laboratory Computerized Systems

by Judy Samardelis and Winnie Cappucci

Background

Risk management concepts in the healthcare industries have matured and harmonized over the years as reflected in ICH Q9 Quality Risk Management. The use of risk management is now an expectation in all aspects of our business. GAMP 5 provides guidance in applying these concepts to the development, implementation, and maintenance of computerized systems. As emphasized in both GAMP 5 and the article written by Kevin Martin and Randy Perez, GAMP 5 Quality Risk Management Approach,[1] "risk to the patient and product quality are the primary points of concern."

This article provides an actual case study that addresses the risk management of computerized systems supporting different regulated business processes. As stated in the article referenced above, "It should be possible to reduce or eliminate unwarranted work at all risk levels, but especially on low risk areas, freeing critical resources to mitigate higher risks." Thus focusing the most effort on computerized systems where failures would have the highest risk of impact to the patient, product, or business. Certainly, computerized systems supporting the release of product to market present one of the highest risks to patient safety and product quality. A simple system that generated an incorrect result for a release assay could compromise patient safety.

Case Study

General

The approach described here is not intended to be a "one-size-fits-all" recipe, but rather one example of a three-phase, five-step process for analyzing the risks associated with the use of computerized laboratory instruments in a regulated business environment. Applying risk management throughout the instrument lifecycle from concept to retirement will increase reliability and enhance patient safety and product quality.

Business risk, patient safety and product quality, data integrity, and the system's functionality are evaluated and assessed using criticality levels. The criticality levels are assigned prospectively. For those systems defined as medium or low risk, criticality should be reassessed if a functional failure of the system occurs during the validation. Tester misuse of system commands or protocol errors are not considered functional failures.

This article will present how one company developed the risk assessment of a spectrophotometer used in a development laboratory as compared to the same instrument used in a commercial manufacturing site. The outcome is based on the assigned risk definitions and attributes associated with the use of the instrument in the different areas of the business. A spectrophotometer supporting a development manufacturing run will have different risk profile than one supporting commercial manufacturing. Nevertheless, both will impact the business process and require mitigation to reduce the risk of potential safety issues. The risk-based approach facilitates scaleable validation by focusing activities on critical attributes, ensuring the validation effort will be commensurate with the overall risk of the process. Use of the instrument cannot create a greater risk than those inherent to the process supported by the instrument.

Method failures, calibration, and sample preparation are not within the scope of the case

Continued on page 38.

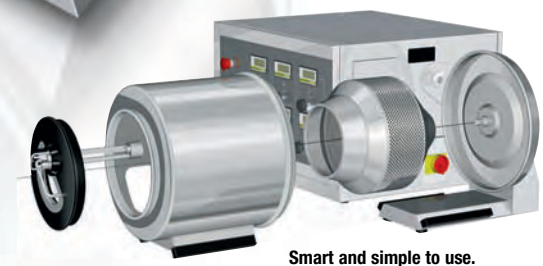
World-Class Tablet Coating in a Bench Top Tablet Coater

GMPC I Mini-Coater

The new GMPC I Mini-Coater makes world-class coating results possible for extremely small batch sizes of 500-2000 g.

With the new Mini-Coater system, you can achieve superior coating at very small batch sizes, thus reducing research and development costs considerably. With three interchangeable pans, the system is extremely flexible and ready for immediate operation.

- Aqueous and solvent processing
- Plug & Play
- Optional qualification package for clinical samples
- Exceptionally attractive price



Smart and simple to use.
The complete housing can be disassembled and reassembled in seconds.

- Fluid Bed Systems
- Vertical Granulators
- Product Handling
- **Pan Coaters**
- Process and Plant Engineering
- Services

Glatt Air Techniques Inc.
20 Spear Road
Ramsey, NJ 07446 / USA
Phone: +1 201 8 25 87 00
Fax: +1 201 8 25 03 89
eMail: info@glattair.com

Glatt GmbH Process Technology
Werner-Glatt-Straße 1
79589 Binzen / Germany
Phone: +49 7621 6 64 0
Fax: +49 7621 6 47 23
eMail: info@glatt.com

www.glatt.com

Glatt®

PE / ISPE – SEPTEMBER / OCTOBER 2009 – NEUBERGER.DESIGN

"…the assignment of business risk is determined by the use or purpose of the test results in the business process. Therefore, knowledge of what the instrument test results are used for in support of the business is crucial."

Phase 1	Risk Analysis	Step 1	Defining Business Risk
		Step 2	Defining Risk to Patient Safety, Product Quality
Phase 2	Risk Evaluation	Step 3	Defining the Criticality of the Instrument Functions
Phase 3	Risk Control	Step 4	Validation and Assignment of Appropriate Controls
		Step 5	Monitoring Controls

Table A. The process flow for the three-phase, five-step process.

study described here. It is assumed that sample preparation and controls are in place and utilized. For guidance on calibration, please refer to the *GAMP Good Practice Guide on Calibration Management*.[3]

In order to achieve success, the following are prerequisites:

1. documented understanding of the fundamental business processes
2. established and accepted definitions of risk levels
3. meaningful assignment of the probabilities that undesirable events could occur
4. defined strategies for testing and mitigation

This case study will rely on the criteria used in a Quality Risk Management Process and the following five questions suggested by *GAMP 5*:[2]

1. What are the hazards or risks that could lead to harm because failure of instrument functionality? It is assumed that the instrument failure produces erroneous test results.
2. What is the impact of the failure? How critical is the instrument in the GxP process? What is the potential harm if affected products are released for use based on erroneous data, either commercially or clinically?
3. What is the probability of the failure? The impact and probability of the failure must be fully understood in the context of the business use to allow for a proper designation of high, medium, or low criticality.
4. Because probability of failure and likelihood of detection are difficult to accurately predict with a new computerized system, quantitative estimates are utilized to facilitate decisions. These assumptions can be evaluated during the validation activities.
5. Can measures be put in place to avoid the failure? Can errors from the failure be detected at other points in the business process before harm to the patient or business occurs?

Quality Risk Management Process Description

The process flow for the three-phase, five-step process is outlined in Table A.

Phase 1, Step 1 – The assignment of business risk is determined by the use or purpose of the test results in the business process. Therefore, knowledge of what the instrument test results are used for in support of the business is crucial. The business risk is assigned as high, medium, or low and is defined in Table B.

Phase 1, Step 2 – The assignment of risk to patient safety can be based on the history of the reliability and data integrity of the laboratory instrument test results if they exist. For new instruments, the manufacturer specifications can be utilized to identify functions that impact patient safety or product quality. The risk to patient safety is assigned as high, medium, or low, as described in Table C.

Business Risk Level	Definition	Additional Attributes to Consider
High	The instrument produces a result that could impact the manufacturing business process in a manner leading to significant long-term detrimental effects and/or potentially catastrophic short-term effects such as product recall or batch rejection.	- Interruption to production schedule. - No redundancy available. - Significant reduction in service level. - Complete loss of confidence on behalf of the customer. - Environmental impact.
Medium	The instrument produces a result that could impact the manufacturing business process in a manner leading to short-to-medium-term detrimental effects, such as delay of batch release or loss of partial batches. This includes instruments used only for in-process testing and redundant systems.	- Business adjustments to laboratory operations required, preventing interruption to production schedule. For example, overtime, third party contracts. - Cost of redundancy is significant, e.g., back up/replacement systems, contract laboratory, etc. - Unavailability of the system will significantly reduce the level of service and/or customer satisfaction.
Low	The instrument produces a result that has no substantial effect on the manufacturing business process. The analyst has the ability to perform a repeat of the assay without loss of product or significant delay or system is not used for product testing.	- No impact to production schedule. - System redundancy is available. - No legal liability. - Unavailability of the system will cause no or minimal interruption to service and/or customer dissatisfaction.

Table B. Business risk.

Continued on page 40.

Important technological advances are brewing in the biopharmaceutical industry…

…and advanced high-purity solutions from MKS are behind many of them.

MKS Instruments, a global leader in critical process management and control, develops and manufactures a wide range of products used in today's most sensitive biotech and biopharmaceutical processes. From instruments to control pressure and flow, to ozone generators for sterilization, to stainless steel fittings, filter housings and housing heaters, MKS has the expertise and cost-effective solutions to address the needs of the most advanced bio processes. For information on these and other MKS products, visit us online at **www.mksinst.com/biopharm.**

mks
Technology for Productivity

MKS Instruments, Inc. Phone: 978.284.4000 or 800.227.8766 (USA only) www.mksinst.com/biopharm

"…utilizing the information from Steps 1 and 2, the overall business risk impact is assigned based on the business risk and the risk to patient safety and product quality."

Risk to Patient Safety, Product Quality	Definition	Additional Attributes to Consider
High	The instrument produces a result that has a direct effect on product release or is used for in-process testing to make manufacturing decisions (e.g. spectrophotometer for determining product concentration).	- Unproven technology, new to business process. - May lead to product recall. - May lead to a significant audit observation causing disruption to operations, e.g. Warning Letter, 483. - Supporting data for product quality/product decision-making.
Medium	The instrument produces a result that has an indirect effect on product release or is used for in-process testing, but not as the final release or redundancy is built into the testing (e.g., spectrophotometers used for checking standards, titrators, polarimeters, microbial identification systems).	- Proven technology, but new to the company. - Potential product impact with limited and defined effects. - Efficacy or safety not affected.
Low	The instrument produces a result that has no effect on product release or is used as a screening tool (e.g., spectrophotometers used for checking optical density of microbial cultures).	- Simple and robust systems based on proven technologies. - System error may lead to minor laboratory rework. - Data specific to make and model on system performance available.

Table C. Risk to patient safety, product quality.

Phase 1, Completion – Utilizing the information from Steps 1 and 2, the overall business risk impact is assigned based on the business risk and the risk to patient safety and product quality.

Phase 2, Step 3 – Criticality levels are assigned in Step 3 to individual or grouped instrument functions. Using the results of Phase 1 and the manufacturer specifications, the critical system functions can be identified. The definitions of high, medium, and low criticality functions are listed in Table D.

Criticality	Definition
High	Functions that have a direct impact on data integrity (e.g., general functions of the instrument are typically high criticality).
Medium	Functions that have an indirect impact on data integrity (e.g. network interface for a system that could have the software installed locally, electronic audit trails for systems that use paper records as the official GXP record).
Low	Functions that have negligible impact on data integrity (e.g., ability to save electronic data for systems that use paper records as the official record).

Table D. Criticality of instrument functions.

Likelihood of Occurrence	Definition
High	Occurrence is frequent
Medium	Occurs, but not frequently, has been experienced previously
Low	Occurrence is sufficiently low to cause comment when it happens, almost unknown.

Table E. Likelihood of occurrence.

Likelihood of Detection	Definition
High	Obvious to users, stops process
Medium	May be noticed during testing or review of results
Low	Unlikely to be noticed during normal operation or testing

Table F. Likelihood of detection.

Phase 2, Completion – A risk assessment of the critical system functions can define the initial validation testing strategy for the instrument. The testing strategy should support the mitigation of the risks resulting from instrument usage and potential failure. Residual risks may arise from any functionality that was not addressed during the validation testing or business functionality that the instrument does not provide.

Complex instruments whose technology is new or unproven or where in-house expertise with the system is limited and that have a Phase 1 risk assessment of "medium" will require the same functional risk evaluation as those with "high." It is essential that the evaluation and its outcome is documented to demonstrate that a systematic and logical approach was followed

Phase 3, Step 4 – During the validation activities of Step 4, verification and operational controls are tested. Should the execution of a test fail, the failure is evaluated based on the criticality of the associated system functionality as defined in Table D. The evaluation of the test failure includes an assessment of the likelihood of the occurrence of the failure - Table E. The criticality of the function is then plotted against the likelihood of occurrence to determine the risk classification rating of each function. The likelihood or difficulty of detection is evaluated and defined as high, medium, or low as described in Table F.

Based upon the combination of the risk classification and failure probability and detectability, a test priority is assigned. Test prioritization is used to further focus the validation activities on high risks. This process helps to define the procedural controls or modification of the instrument method to avoid the risk or increase the detectability of the failure in the future. In this process, the validation failures are evaluated to

determine if there is an actual failure in functionality versus execution of the test or test error. To repeat, tester misuse of system commands or protocol errors are not considered functional failures.

Upon completion of the validation activities and implementation of the controls used as mitigation, any residual risk associated with the instrument is assessed and documented. If the residual risk is not acceptable, additional mitigation controls may be implemented until acceptable levels of residual risk are achieved. The validation report documents the results and failures, while providing traceability and evaluation of the likelihood of occurrence and detection. Included in the report is the summary of the subsequent controls implemented to reduce the risk and a concluding residual risk assessment.

Phase 3, Step 5 – The final step of the risk management process is risk control. At a high level, risk control may be effected by:

- avoidance (for example, in the cases of new technology that, upon evaluation, is deemed to be too risky to use)
- mitigation (the approach addressed by this article)
- acceptance of the risk as-is and transfer, whereby the risk is displaced (a unique, business-critical instrument is available only from a single vendor and additional controls may therefore be needed to ensure the accuracy of the result).

Actual Risk Assessment of the Two Spectrophotometers

Here are the results of the Quality Risk Management as applied to two spectrophotometers: one used in a GxP manufacturing facility and the other in a GxP laboratory.

1. Manufacturing Floor

The instrument is used as a screening tool to measure in process product concentration. No effect on product release.

Phase 1 Risk Level of Medium

	Low	Medium	High
Business Risk		X	
Risk to Patient Safety, Product Quality		X	

Phase 2 Risk Level of High

	Low	Medium	High
Criticality of the Instrument Functions			X

Note: As described previously, if the instrument has an overall instrument impact of high, perform a functional risk assessment for each requirement listed in the functional specification document. A detailed functional risk assessment is optional for some medium impact instruments depending upon items, such as proven technology. Simple robust systems or minor rework may be required if the instrument produces erroneous data. If errors occur during validation that had not been considered, a functional assessment can occur at that time, while evaluating the impact of the failure and the potential for detection, etc.

Phase 3 Risk Level of Low

	Low	Medium	High
Likelihood of Occurrence	X		
Likelihood of Detection			X

Overall System Impact Assessment = Medium

	Low	Medium	High
Business Risk		X	
Risk to Patient Safety, Product Quality		X	
Criticality of the Instrument Functions			X
Likelihood of Occurrence	X		
Likelihood of Detection			X

2. GxP Laboratory

Used as a screening tool for checking optical density of microbial cultures. No effect on product release, not used for product testing.

Phase 1 Risk Level of Low

	Low	Medium	High
Business Risk	X		
Risk to Patient Safety, Product Quality	X		

Phase 2 Risk Level of Low

	Low	Medium	High
Criticality of the Instrument Functions	X		

Note: As described previously, if the instrument has an overall instrument impact of high, perform a functional risk assessment for each requirement listed in the functional specification document. A detailed functional risk assessment is optional for some medium impact instruments, depending

Concludes on page 43.

"Each organization must determine the criteria surrounding the use of a laboratory computerized system in the business process when defining the risk to patient safety and the business process should a failure occur."

upon items, such as proven technology. Simple robust systems or minor rework may be required if the instrument produces erroneous data. If errors occur during validation that had not been considered, a functional assessment can occur at that time, while evaluating the impact of the failure and the potential for detection, etc.

Phase 3 Risk Level of Low

	Low	Medium	High
Likelihood of Occurrence	X		
Likelihood of Detection			X

Overall System Impact Assessment = Low

	Low	Medium	High
Business Risk	X		
Risk to Patient Safety, Product Quality	X		
Criticality of the Instrument Functions	X		
Likelihood of Occurrence	X		
Likelihood of Detection			X

Summary

Each organization must determine the criteria surrounding the use of a laboratory computerized system in the business process when defining the risk to patient safety and the business process should a failure occur. Monitoring of the instrument's performance and the effectiveness of the applied controls for mitigation should occur as part of the periodic review process in accordance with the organizations' pre-determined periodic review process.

References

1. Martin, K.M. and Perez, A.R., "GAMP 5 Quality Risk Management Approach," *Pharmaceutical Engineering,* May/June 2008 Vol. 28, Number 3, pp.24-34.
2. *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems,* International Society for Pharmaceutical Engineering (ISPE), Fifth Edition, February 2008, Section 5 – Quality Risk Management, www.ispe.org.
3. *GAMP® Good Practice Guide: Calibration Management,* International Society for Pharmaceutical Engineering (ISPE), First Edition, December 2001, www.ispe.org.

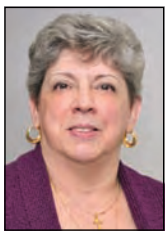
Acknowledgements

I would like to express my gratitude to the members of the GAMP Risk Management SIG and GAMP Steering Committee who reviewed and provided substantive comments during the development of this article.

About the Authors

Judy Samardelis has been in the industry more than 17 years in various roles of quality control, study director of preclinical studies, drug delivery, assay development, and validation, including several years specializing in computer and laboratory validation using GAMP® methodology in support of several Wyeth Biotech sites. In her current role, she has successfully implemented a Qualification Program for Statistical Applications using a risk-based approach as well as development of a PQ by Exception methodology to streamline validation activities. She is Co-Chair of the GAMP® Risk SIG team, member of the GAMP Steering Committee, and Co-Chair of the *Pharmaceutical Engineering* Committee. She is also a member of the GAMP® COP, PAT COP, and C&Q COP. Samardelis has a BA in microbiology from the University of New Hampshire, Durham. She can be contacted by email: SamardJ@wyeth.com.

Wyeth BioTech, 1 Burtt Rd., MS-F1100, Andover, Massachusetts 01810-5901, USA.



Winnie Cappucci has worked in the pharmaceutical industry for 40 years. She has worked as a business process owner designing and testing computerized systems for 10 years. She also worked as an IT professional with thorough knowledge of software development life cycle and computerized system operations and support for 12 years. For the last 18 years, Cappucci has worked as a quality and compliance computer validation specialist in a highly regulated environment. She has diverse software and computerized system validation and auditing experience. She is a member of the GAMP America Steering Committee and the GAMP Editorial Board. She also is a member of the PDA Industry Advisory Board for Technical Report 32 (Auditing of Suppliers Providing Computer Products and Services for Regulated Operations). She can be contacted by email: winnie.cappucci@bayer.com.

Bayer Healthcare, 6 West Belt, Wayne, New Jersey 07470-7358, USA.

... because calibration is a matter of confidence

AMETEK®
CALIBRATION INSTRUMENTS

Why AMETEK Calibration Instruments?

- **We offer a complete line of instruments for temperature, pressure, and signal calibration providing the highest accuracy and quality to optimize your process.**
- **We have more than 50 years of experience - use it!**

North American contact: Tel: +1 800 527 9999 • E-mail: cal.info@ametek.com

Worldwide contact: Tel: +45 4816 8000 • E-mail: ametek@ametek.dk

Find more info at www.jofra.com

Latin America

Brazil

New Certified Reference Substance[1]

Resolution RDC 32 has established a new reference substance, ceftriaxone sodium, according to studies of certification coordinated by the Comissão Permanente de Revisão de Farmacopéia Brasileira (CPRFB). The use of this reference substance is mandatory for the manufacture and quality control of raw materials and medicinal products that must be compared to a reference substance. This resolution became effective on 9 June 2009.

Mexico

GMP[2]

The Mexican Norm NOM-059-SSA1-1993 provides information on Good Manufacturing Practice for establishments of the pharmaco-chemical industry involved in the production of medicines. It includes definitions of relevant terms, the requirement for the design and organization of an establishment in the chemical/pharmaceutical sector, manufacturing control, manufacturing equipment, technical and legal documentation, destruction of waste and residues, and the classification of different areas. The modifications to this norm include explanation of which institutions/organizations took part in the development of this Norm; deviations or non compliance; devolutions and complaints; recalls, validation, change control, and technical audits. These chapters follow the US Code of Federal Regulations, Parts 210 and 211.

This Norm replaces Official Mexican Norm NOM-059-SSA1-1993 and became effective on 19 June 2009.

Europe

Austria

Decree on Trade and Consumption of Narcotics[3]

The Decree on Trade and Consumption of Narcotics (374/1997) provides information on the production, manufacturing, transformation, purchase, possession, and delivery of narcotics and their corresponding authorization. It also details the required documentation for producers, wholesalers, manufacturers, doctors, dentists, and pharmacists; as well as the requirements for packaging; prescription and delivery; maximum quantities allowed. For medicinal products containing narcotics, it details the first aid and substitution therapy; export and import licenses; facilities of the United Nations located in Vienna and transitional provisions. This Decree on Trade and Consumption of Narcotics has been amended to include new substances.

Ireland

Quality Defect Investigation Reports[4]

The Irish Medicine Board (IMB) have released a guide to address the format and content required for quality defect investigation reports for medicinal products.

The following categories are included in the guide: medicinal products which are the subject of a Marketing Authorization (MA) or registration; medicinal products manufactured in Ireland which are distributed in Ireland or elsewhere; medicinal products distributed inside and outside the EU by Irish wholesalers and exporters; promotional samples of medicinal products issued to healthcare professionals; exempt medicinal products for human use which are supplied to the order of a registered doctor or a registered dentist for use by his/her individual patients under his/her direct personal responsibility, or in the case of unauthorized veterinary medicinal products, medicinal products supplied in accordance with the cascade system; investigational medicinal products manufactured and distributed for the purposes of performing clinical trials.

Turkey

Required Documentation and Conditions for Opening Manufacturing Sites[5]

This document published by the IEGM General Directorate of Pharmaceuticals and Pharmacy, provides the list of documents and conditions required for the opening of manufacturing sites of medicinal products, active ingredients of medicinal products and intermediate products, according to the provisions of the By-Law on the Manufacturing of Pharmaceutical Products.

The required documentation are from the General Director of the manufacturing site; responsible person(s) of manufacturing; responsible person(s) of quality control; responsible person or team of quality assurance; manufacturing site; SOPs regulating the activities of the manufacturing site; particularities of the water and aeration system together with a plan; original or notary-approved document of the authorization of non-hygienic establishment; report on the evaluation of the environmental impact and proof of fee payment.

EMEA Updates

DG ENTR Conclusions on Study on Pharmaceutical Excipients[6]

Following the publication of a report on an impact assessment study at the beginning of June 2009 by an external contractor, DG Enterprise and Industry has taken the decision not to continue with the preparation of a Commission Directive on GMP for certain excipients as originally foreseen in Article 46(f) of Directive 2001/83/EC.

Reference Medicinal Product[7]

On the 18 June 2009, the European Court of Justice ruled that Directive 2001/83/EC is to be interpreted as meaning that a medicinal product which falls outside the scope of Regulation No. 726/2004, and the placing of which on the market in a Member State was not authorized in accordance with the applicable Community law, cannot be considered to be a reference medicinal product within the meaning of Article 10(2) (a) of Directive 2001/83.

The Court stated that to allow a medicinal product benefiting from an authorization issued on the basis of national provisions alone to be considered to be a reference medicinal product would amount, in fact, to authorizing an exception to the rule, laid down in particular in Article 6(1) of Directive 2001/83 that a medicinal product which has not been authorized in accordance with Community law may not be placed on the market of a Member State.

Transgenic Animals in the Manufacture of Biological Medicinal Products[8]

On 25 June 2009 the EMEA released a concept paper to propose a revision of the Guideline on the Use of Transgenic Animals in the Manufacture of Biological Medicinal Products for Human Use.

The current guideline became effective in July 1995 and the production method for recombinant proteins is transgenic animals has progressed significantly. This revision aims to adapt aspects of the quality guidance already in place for other production systems to the special case of transgenic animal systems.

Variations (codecision part): Publication of Amendments to Directive 2001/82/EC and Directive 2001/83/EC[9]

A new Directive 2009/53/EC has been published in the Official Journal on 30 June 2009 regarding variations to the terms of marketing authorizations for medicinal products. This Directive is part of a global revision of the legal framework on variations to make the overall system clearer, simpler, and more flexible, and it amends the legal basis for the adoption of Community rules on variations in order to harmonize those rules for all authorized medicines in the EU.

Asia

China

Verification and Inspection of Accreditation of Clinical Trials[10]

This notification is issued to stipulate the goals, timeline requirements, procedures, and criteria for verifying, inspecting, and re-granting the accreditation for clinical trial sites qualified by governments.

All clinical trial sites must be qualified by China State Food and Drug Administration (SFDA) and the Ministry of Health (MoH). When this is not the case, the site cannot participate in any Phase I to Phase III studies for any therapeutic fields. The accreditation is valid for three years and before the accreditation validity, China SFDA needs to re-verify and inspect each accredited site and see if they are up to the standards.

There are currently 325 clinical trial sites (hospitals) qualified for drug clinical trials in China.

International

WHO

Procedure for Assessing the Acceptability, in Principle, of Active Pharmaceutical Ingredients for use in Pharmaceutical Products[11]

The World Health Organization (WHO) released the Annex 4: Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products.

This quality assessment procedure is to evaluate whether APIs meet the requirements recommended by the WHO, and that they are manufactured in compliance with WHO good manufacturing practices. This will be done through standardized quality assessment and inspection procedures.

Continued on page 46.

Australia

Therapeutic Goods Charges Regulations 1990: Fees[12]

The Therapeutic Goods Agency (TGA) amended The Therapeutic Goods (Charges) Regulations, which prescribes the annual fee for the registration and listing of therapeutic goods and licensing of manufacturers of therapeutic goods as imposed by the Therapeutic Goods (Charges) Act. This became effective on 10 July 2009.

Canada

Proposed Amendment: Adverse Drug Reaction Reporting[13]

Amendments to Division 1 of the Food and Drug Regulations have been proposed in order to require manufacturers to notify the Minister of a significant safety signal arising from the annual summary report. The amendment also will clarify when the Minister can request case reports or summary reports and enable the Minister to request case reports or summary reports when they consider it necessary to establish the safety of a drug under the conditions of use recommended.

United States

cGMP[14]

A Questions and Answers document, Level 2 guidance, providing answers to questions and clarifying existing requirements and policy regarding current Good Manufacturing Practices (cGMPs) for human, animal, and biologics medicinal finished products has been published. This guidance has been updated with questions and answers relating to equipment, control of components and drug product containers and closures, production and process controls, laboratory controls, records and reports, and has been updated with a cGMPs penicillin drugs section.

Incorporation of Physical-Chemical Identifiers into Solid Oral Dosage Form Drug Products for Anti-counterfeiting[15]

On 14 July 2009, the Food and Drug Administration (FDA) released a draft guidance that details recommendations to pharmaceutical manufacturers on design considerations for incorporating Physical-Chemical Identifiers (PCIDs) into Solid Oral Dosage Forms (SODFs).

The guidance provides supporting documentation to be submitted in New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs), to address the proposed incorporation of PCIDs in SODFs,

It also includes supporting documentation to be submitted in post-approval submissions to report or request approval to incorporate PCIDs into SODFs, and procedures for reporting or requesting approval to incorporate PCIDs into SODFs as a post-approval change.

This draft guidance also provides FDA recommendations regarding evaluation of toxicological and other concerns for PCIDs that are incorporated into packaging and labeling and procedures for reporting or requesting approval to add PCIDs to packaging and containers as a post-approval change.

Abbreviated New Drug Applications ANDAs – Impurities in Drug Substances (Revision 1) (Final)[16]

This FDA released guidance details recommendations on Chemistry, Manufacturing, and Controls (CMC) information to be included in the report submitted on acceptance criteria for residual solvents in drug substances and products. This guidance is aimed in particular to products proposed in original Abbreviated New Drug Applications (ANDAs), Drug Master Files (DMFs), including type II DMFs, and related supplements.

Recommendations for establishing acceptance criteria for impurities in drug substances also are provided in this guidance as well as information regarding identification and qualification of impurities in drug substances.

This document replaces the Draft Guidance for Industry: ANDAs: Impurities in Drug Substances (Revision 1), Jan-2005.

Labelling Change for Leukotriene Modifiers[17]

On 12 June 2009, the FDA requested manufacturers to include warnings in the drug prescribing information for SINGULAIR (montelukast), ACCOLATE (zafirlukast), ZYFLO and ZYFLO CR (zileuton), asthma drugs known as leukotriene modifiers. This request follows neuropsychiatric events that have been reported to the FDA, such as anxiousness, mood changes, or suicidal behaviors.

Leukotrienes are substances in our bodies thought to cause allergy and asthma symptoms. Leukotriene modifiers work by blocking leukotrienes or by stopping the formation of certain substances that cause swelling, tightening, and mucus production in the airways.

Immunosuppressant Drugs: Labeling Changes[18]

On 14 July, the FDA published a document in order to require that manufacturers of RAPAMUNE (sirolimus), SANDIMMUNE (cyclosporine), NEORAL (cyclosporine modified), CELLCEPT (mycophenolate mofetil), and MYFORTIC (mycophenolic acid) to update labeling to include stronger warnings, about the risk of opportunistic infections, such as activation of latent viral infections, including BK virus-associated nephropathy. This FDA requirement is a result of analyses conducted by the FDA of its Adverse Event Reporting System (AERS) that emphasized the association between BK virus-associated nephropathy and the use of these immunosuppressant drugs. These drugs are used to protect against the rejection of certain organ transplants, and have been associated with BK virus-associated nephropathy, and other infections, which may lead to serious outcomes, such as renal allograft loss.

References

1. Diário Oficial da União (DOU), Legislation, Official Journal, No. 108 of 09-Jun-09 (Section 1, p.47), http://www.in.gov.br.
2. Diario Oficial de la Federación, (DOF): 22-Dec-2008.
3. Bundesgesetzblatt, Legislation, Official Journal, Teil II, Nr. 173/2009 vom 15. Juni 2009, http://www.digitalegesetze.at.
4. Agency, IMB, Medicines Agency, http://www.imb.ie.
5. Agency, IEGM, Medicines Agency, http://www.iegm.gov.tr.
6. EMEA update, 09 June 2009, http://www.emea.europa.eu/.
7. EMEA update, 18 June 2009, http://www.emea.europa.eu/.
8. EMEA update, 25 June 2009, http://www.emea.europa.eu/.
9. EMEA update, 30 June 2009, http://www.emea.europa.eu/.
10. SFDA, http://eng.sfda.gov.cn/eng/.
11. http://www.who.int.
12. Obtained from the Commonwealth of Australia Law (ComLaw) Web site, http://www.comlaw.gov.au.
13. Canada Gazette / Gazette du Canada, Legislation, Official Journal, I Volume 143, No 24, 13-Jun-09, http://www.canadagazette.gc.ca/PartI.
14. Agency, CBER, CBER, CDER, CDER, CVM, CVM, Center, FDA, Medicines Agency, ORA, http://www.fda.gov/cder.
15. Agency, CDER, CDER, Center, FDA, Medicines Agency, Volume 74, Number 133/Pages 34021 – 34022, Docket No. FDA-2009-D-0212, http://www.accessdata.fda.gov.
16. Agency, CDER, CDER, Center, FDA, Medicines Agency, http://www.fda.gov.
17. Agency, FDA, Medicines Agency, http://www.fda.gov.
18. Agency, FDA, Medicines Agency, http://www.fda.gov.

This information was provided by Frank Sayala, Pharmaceutical Research Associates (UK).

This article will describe Building Information Modeling (BIM), provide several real-world examples of the advantages that owners have experienced when their projects were designed and developed with BIM, and offer suggestions for minimizing risks and maximizing BIM's benefits.

Enhancing Delivery of Complex Facilities with Building Information Modeling (BIM) Technology

by Andrew Signore, P.E., CPIP and Stephen R. Franey, RA

In a market that places tremendous cost, time, and performance pressures on building owners, an innovative project delivery technique could conceivably help reduce construction costs by up to 10 to 15 percent by improving constructability and reducing waste. Implementing this innovative technique also could reduce construction time for complex projects by as much as 15 to 25 percent by supporting better coordination and more organized project delivery. Building Information Modeling (BIM) technology represents a new approach to architectural and engineering design that can deliver a multitude of benefits around the delivery of complex projects, including lower first costs, compressed construction timelines, and reduced operational costs. Full-color, digital, three-dimensional models that are updated in real-time make it easier for the owner to understand and visualize the project and make decisions as an active participant on the project team. BIM's benefits don't end with the ribbon cutting, but extend throughout the project lifecycle. BIM's more robust, more accurate project documentation enables owners to operate the facility with greater clarity and continued cost savings.

This article will describe Building Information Modeling (BIM), provide several real-world examples of the advantages that owners have experienced when their projects were designed and developed with BIM, and offer suggestions for minimizing risks and maximizing BIM's benefits.

A New Approach to Architectural/Engineering Design and Construction

Project owners need speed to market and control of capital costs. The traditional way of designing, building, and delivering complex facilities – with separate silos and inherently fragmented communications – creates time and cost inefficiencies that owners can't afford. Conceived about a decade ago, BIM is a novel way of working on projects that allows coordinated, consistent information to help owners make decisions faster; provides better documentation at all levels; and enables model simulations that make it possible to predict performance prior to construction.

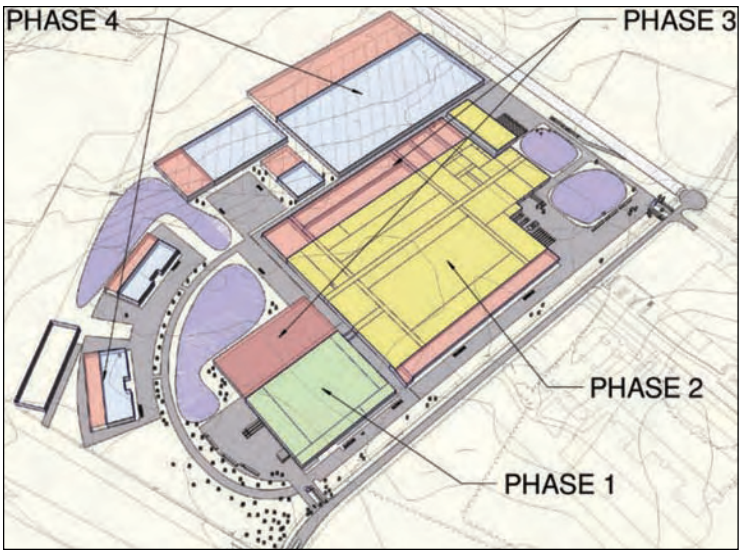
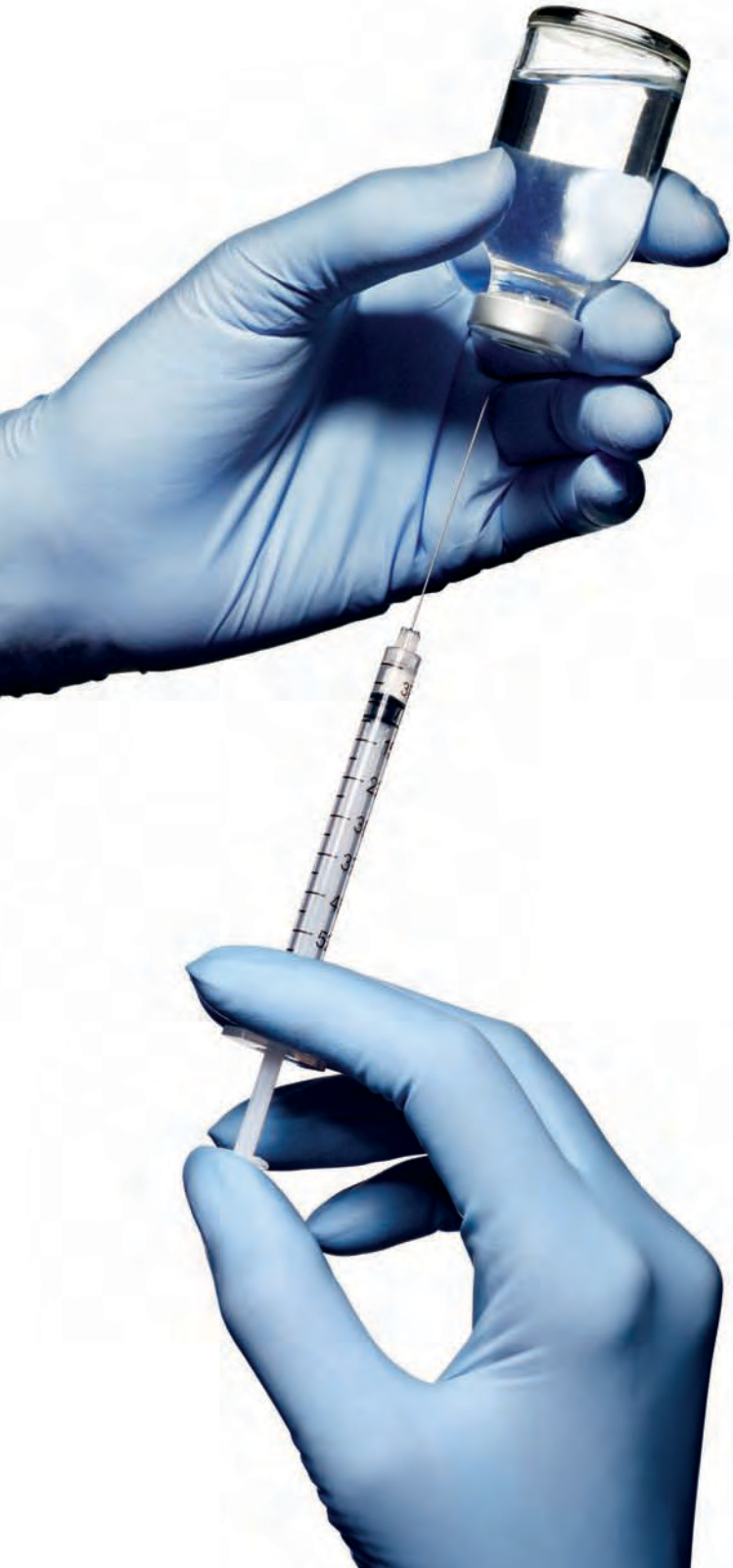


Figure 1. Multi-phased campus master planning through the use of BIM.

BIM is both a process and a design tool that provides a way to share building information among project team members through a database recognized as a 3D model. It

Continued on page 50.

A healthy injection for your business



Rather than treating individual production symptoms, protect your business with:

- Comprehensive documentation packages to ensure easy validation
- Robust, reliable and repeatable performance at any scale
- Ease of cleaning and maintenance
- Minimized risk and maximized uptime

For more information or to contact a local representative visit www.alfalaval.com/biopharm

ALFA LAVAL

www.alfalaval.com/biopharm

ESE01553BEN 09/07

helps the architecture, engineering, and construction (A/E/C) teams and the owners communicate more easily and clearly for better project management, coordination, and schedule integration. BIM use is growing throughout the A/E/C industry. The US General Services Administration (GSA) now requires the use of BIM for all GSA-funded capital projects. BIM software includes applications such as AutoCAD® Revit® Architecture Suite, Bentley BIM, Vectorworks Architect and ArchiCAD START. BIM organizes complex projects and improves visualization and communication for all stakeholders to a degree never before possible.

Historically, architects and engineers worked in a manually intensive environment. When Computer Aided Design (CAD) software was introduced in the early 1960s, it automated drawing tasks, but the CAD mindset still revolved around the concept of hand drafting. BIM represents the next step in the evolution of CAD. BIM technology gives designers a new level of creative control by enabling them to build a virtual 3D model. BIM combines true 3D visual studies with real-time construction documents in a single database that manages all aspects of the model. In this, BIM far outstrips the capabilities of two-dimensional CAD systems and even conventional 3D design systems, neither of which can manage a database.

BIM makes it easier to evaluate and communicate the impact of design changes, which helps minimize unexpected cost increases and construction delays. During the master-planning phase of a 76,000 square foot research and development facility, BIM enabled the design team to develop a number of alternative approaches very quickly and to communicate them with such clarity and simplicity that the owner could easily differentiate and make a decision. The designers were able to input project-related data, such as validation master planning criteria and other critical parameters, into the BIM database in parallel with the building model design.

BIM also allows the project team to explore the fourth dimension – time. For example, a team using BIM optimized construction scheduling for a new two million square foot engine assembly plant and enabled on-schedule completion of all milestones on an aggressive project schedule to meet the owner's timeline. BIM enhanced coordination among the trades by generating visually descriptive documentation that provided a better understanding of components and systems. A better understanding of component relationships can help reduce scheduling conflicts so, for example, the contractor who is installing the sprinkler isn't scheduled when the electrician is working. BIM also can be linked with Microsoft Project data.

Additionally, the designer and owner can take a "virtual walk-through" of the model. For example, it's possible to develop ergonomic studies with end users during the conceptual design phase or to check the model to make sure that end users can access valves, panel or other maintenance elements once the project is constructed. For an R&D facility in the Midwest, BIM enabled virtual laboratory development. Immersed in the virtual model, the designer and owner reviewed the space, lab equipment, casework, and utilities and made real-time changes. Using this approach on projects can streamline the design process and ultimately reduce construction confusion – leading to fewer construction delays and less rework with its associated costs.

BIM automates routine tasks, so architects and engineers can spend more time making the design more robust. Designers "build" the entire project - inside and out - from elements in a centralized project database. Many standard objects, such as "smart" 3D doors and windows, can be downloaded from their respective vendors. If the designer replaces one element with another, BIM instantly makes the change throughout the project drawings and documents, on floor plans, section views, building elevations, material schedules, etc. For highly specialized equipment, the architect/engineer also can build custom 3D objects based on vendor specifications. Vendor data is embedded within the object.

BIM's parametric capabilities and bidirectional workflow make it easier to accommodate last-minute changes to the design without significantly delaying the project schedule. "Parametric capabilities" refer to the fact that each object, such as a 3D door, in the BIM database has certain dimensional constraints associated with it that allow it to be resized. If the designer changes a dimension on a single door, BIM instantly changes the size of that specific door and simultaneously updates any associated 3D model and/or parameter information as required. Additionally, BIM's bidirectional workflow allows designers to make multiple changes at a single point in the model. If the designer changes the size of a specific door, BIM changes the size of that particular door anywhere else that it is used in the model. Together, they allow greater speed and flexibility. As a case in point, the day before the construction issue for a recent project was to be sent out, the owner wanted to extend out an exterior wall by 10 feet. The designer only had to make the change to the wall once on a floor plan drawing sheet. The model adjusted the roof, the floor, and other impacted components and automatically updated all drawing sheet views and schedules. The change was made in seconds rather than hours, as would have been the case with traditional CAD software, because the designer did not have to update each drawing sheet manually.

Additionally, team members at various geographic locations can work in the same BIM project database simultaneously. Remote users simply create a "local" file at their current location; this local file links back to the main BIM project. With real-time updates, project documents are always current. For owner and designer, this obviously saves time over having to send a single set of CAD drawings from one office to another. Smaller offices can work as if they were one large office. This arrangement is particularly beneficial for owners with complex projects that are typically too large for a single small office to handle.

BIM also gives the owner convenient access to all building information in an electronic format that is easier to search and store than dozens of boxes of documentation from the design and construction teams. The owner can use the model for future analysis and/or for projects associated with the project.

BIM Offers Operational Advantages

A BIM facility should cost the owner less to build and operate

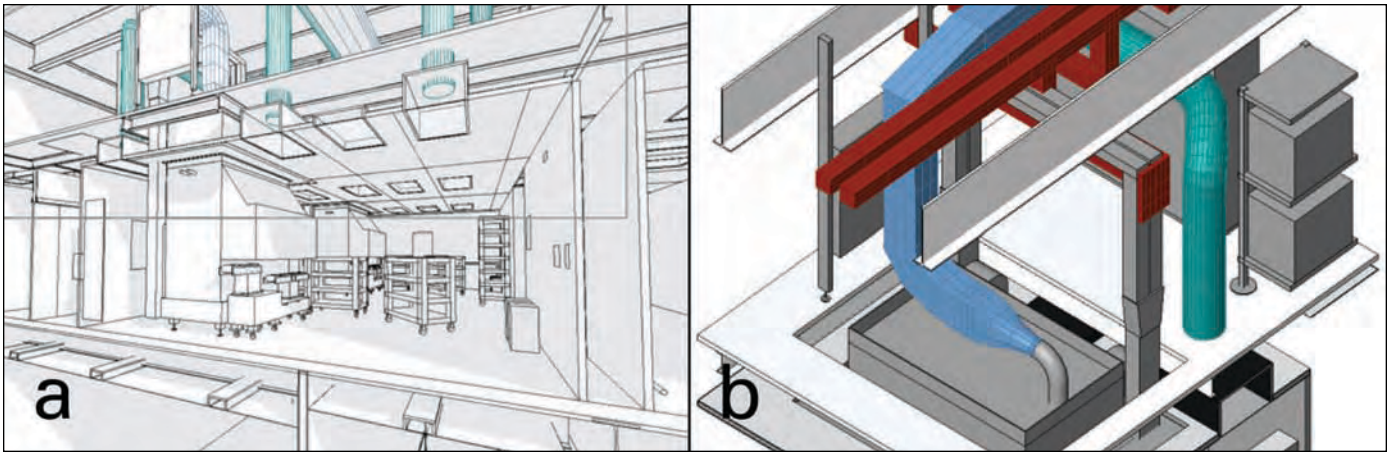


Figure 2a and 2b. BIM technology provides 2D and 3D views and allows for interference checking or "clash detection" reports.

than a conventionally designed building. For one, BIM facilitates more energy efficient design and supports analysis of building lifecycle behaviors. BIM can track utility requirements associated with each piece of material and/or equipment. The A/E professional can see all the requirements and totals for utility loads, for example, so equipment choices can be optimized during the design phase. BIM's "bill of materials" and quantitative material reports support in-house estimating teams.

Certain plug-ins make it possible to use BIM to assess whether the building meets requirements for LEED® certification by calculating the volume of sustainable materials used in construction, all driven by the project database. Used with BIM, web-based and third-party applications, such as Autodesk® Green Building Studio®, ECOTECT, and IES's Virtual Environment further analyze the building's envelope and make-up so the design team can provide solutions that best meet the owner's desire for sustainability and "green" building analysis and construction.

Owners could use model data to help reduce maintenance costs through greater accuracy and efficiency. The wealth of information in the project database can simplify record keeping and provide greater clarity regarding building components

Continued on page 52.

and system configurations. This information remains easily available to the owner, who can download it or access it via the Internet to use for facility management – like a stick-built model for the 21st century. Just as it does during the construction process, the model provides a level of visualization that facilitates everything from ordering parts to staging major upgrades, renovations, or plant shutdowns. For example, if it's necessary to pull out a chiller, the 3D model makes it possible to see exactly what equipment would have to be moved and how the area could be accessed. BIM also enables ergonomic analysis of equipment, which can provide owners with valuable information to help protect the workforce from injury.

A Different Way to Look at Things

BIM enables owners to "see" the facility long before ground is ever broken. BIM generates a three-dimensional virtual model, and not just a series of 2D representations, so it raises visualization, communication, and collaboration to new heights. Ultimately, this helps increase accuracy and reduces project costs and schedules. All members of the project team can view the BIM model remotely via the Internet, saving travel time and costs. Owners can take a virtual walk-through of the facility regardless of where in the world they are in relation to the facility, or to the design firm. BIM also provides the ability to explore "what-if" scenarios, quickly review options for architectural elements, and make changes on the fly. The designer can create camera views of interior rooms to show the owner exactly where equipment will be placed. In a research laboratory, for example, the level of detail can extend down to fume hoods, microscopes, mass spectrometers, High-Performance Liquid Chromatography (HPLC) units, sinks, etc. This capability lets the owner examine and understand ergonomic issues long before construction begins. Being able to see and compare the options in three dimensions makes it easier to make decisions.

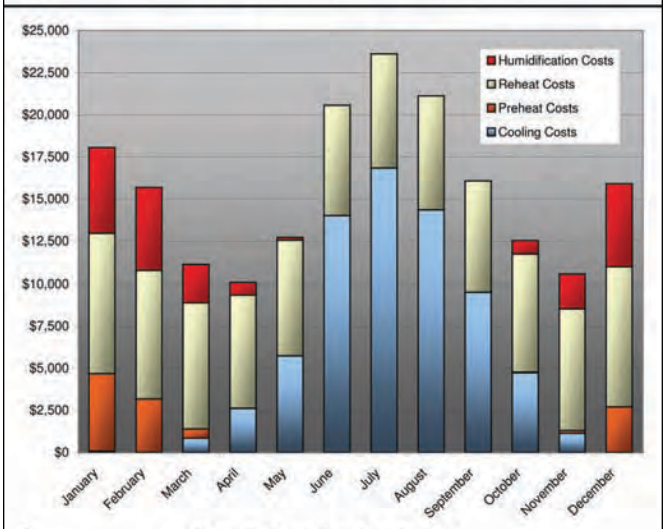
Although builders and subcontractors may be more accustomed to visualizing a finished project based on floor plans and building elevations, they benefit from BIM as well. The 3D model provides a clearer understanding of how the project comes together and helps eliminate unknowns and surprises so they can estimate costs and timelines more accurately – and often more quickly. Third-party estimating software, such as Innovaya's Visual Estimating package, allows builders to import the BIM model to generate accurate pricing and material take-offs.

BIM Technology Can Help Lower First Costs

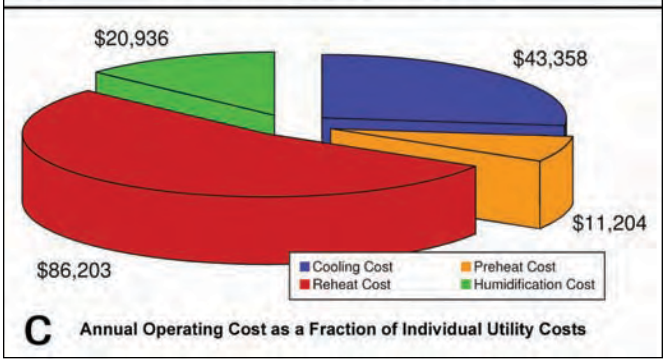
Using BIM offers several advantages, which all add up to better cost control for complex capital projects. Getting enough input to develop the model requires early decision-making and a lot of communication – which brings an exceptional level of clarity to the design process. As the model is being built, designers can use BIM to double-check to ensure that the building meets the owner's goals. For example, using parametric models of robotic assembly equipment made it possible to optimize the size of a manufacturing facility to accommodate the equipment without making it so large that it generated excessive utility costs. Reaching this degree of precision in the early stages defines the project scope much more clearly for everyone, so it is easier to keep the project team on target. When changes are required, BIM makes it easier for the owner to understand the impact of those changes – on the building

Month	Cooling Cost	Preheat Cost	Reheat Cost	Humidification Cost	Total Cost
	$	$	$	$	$
January	$23	$4,596	$8,271	$5,102	$17,993
February	$0	$3,167	$7,644	$4,870	$15,681
March	$300	$531	$7,501	$2,289	$10,620
April	$1,042	$8	$6,737	$757	$8,544
May	$2,647	$2	$6,815	$168	$9,632
June	$9,491	$0	$6,565	$0	$16,056
July	$12,115	$0	$6,784	$0	$18,900
August	$9,612	$0	$6,784	$0	$16,396
September	$5,142	$0	$6,565	$0	$11,707
October	$2,605	$38	$6,982	$794	$10,418
November	$381	$167	$7,225	$2,080	$9,853
December	$0	$2,697	$8,329	$4,874	$15,900
Total	**$43,358**	**$11,204**	**$86,203**	**$20,936**	**$161,700**

a Monthly Operating Costs per Utility



b Monthly Operational Costs as the Summation of Individual Monthly Utilities



c Annual Operating Cost as a Fraction of Individual Utility Costs

Figures 3a, 3b, and 3c. The building envelope data created by the architect is easily extracted from the model by the mechanical team for multiple energy analysis. The architect can site new buildings not only based upon traffic flow and aesthetics and optimally orient the building so as to maximize the energy performance of the building's HVAC systems in response to solar impact as well. This project involved roughly 40,000 square feet of GMP warehouse and secondary packaging space.

and its systems, as well as on costs and timelines.

It is generally accepted that a portion of building materials for any project may be wasted. Some of this waste is due to the fact that, when the project is built from conventional 2D CAD drawings, drawing sets are either inaccurate or not developed enough to show the full extent of the interaction between the various Mechanical/Electrical/Plumbing (MEP) systems. As a result, sections often need to be reworked in the field, which costs extra time and money. BIM can help reduce the need for costly and wasteful rework by helping reduce the occurrence of such surprises. BIM's ability to run "clash detection" reports identify potential conflicts between the different disciplines. Clash detection reports show potential conflict areas in the building during the design process. Unlike a CAD drawing, a BIM model alerts designers when they are trying to put ductwork where pipework needs to run. The unique 3D model shows how the finished building "works." The designer can then change the model until all conflicts are resolved. By helping reduce the amount of material that is potentially wasted, this process translates directly into cost savings. This capability can be particularly valuable for complex facilities with intensive Mechanical/Electrical/Plumbing (MEP) requirements and highly specialized equipment. BIM plug-ins exist to allow designers to check Heating/Ventilation/Air Conditioning (HVAC) volumes and calculations based on the project model.

BIM allows for more accurate cost projections, because designers can develop accurate materials schedules. Even using CAD, designers are limited by how much information they can generate and track within a given amount of time. With BIM, once the model is built, the software automatically generates sections, elevations, and floor plans. BIM also streamlines material takeoffs, and it can even integrate the design with the project schedule. Purchasing is based on real-time data.

BIM can help owners get more accurate estimates from contractors and minimize the delays and unplanned costs associated with Requests For Information (RFIs). Projects using BIM usually generate far fewer RFIs, because the necessary information is contained in the model. Builders and subcontractors do not need to keep coming back for more information, and they don't need to build in as many contingencies for unknowns. They can approach the entire process with a better understanding of the work. This tightens up everything from the bid cycle all the way through change orders, which usually follow requests for information.

The reduction in RFIs was clearly demonstrated with a highly complex manufacturing facility that was completed successfully using BIM. A project of this size (25,000 square feet) and complexity typically might involve 50 to 80 RFIs. Following the design phase, the architectural design team and the construction management team used BIM to reduce the total RFI log to approximately 10 RFIs with no change orders because all stakeholders had a clear understanding of

Continued on page 54.

what the project involved. In fact, for this owner, the project represented a record low for RFIs, rejected submittals, and change orders for a project of this size.

BIM Supports Shorter Construction Cycles

Shortening construction cycle time can sometimes offer owners strategic advantages, and it is almost always desirable in terms of cost control. Every day in the field has associated costs for supervision, construction managers, labor, trailer rentals, etc. Although BIM frontloads the project with intensive requirements in the planning stages, it can help save costs by streamlining execution. By the time construction starts, everyone on the project team should have all the information they need to proceed. Throughout construction, they can interrogate the 3D model and view the project's traditional 2D shop drawings. The ability to visualize the project in three dimensions, eliminate potential conflicts before construction starts, and understand the impact of potential changes helps all stakeholders work more closely together and supports better buy-in.

When an owner wanted a major expansion of a vaccine production facility, BIM provided the precision in-shop assembly necessary to incorporate prefabricated MEP elements, along with modular walls and ceilings, in order to save construction time. BIM made it possible to coordinate all the disciplines involved with the structural and architectural systems. Key subcontractors for HVAC, electrical, instrumentation, plumbing, and process piping were selected early and met weekly with the design team. This approach made it possible to maximize prefabrication and subcontractors were able to get right to work. Ductwork, piping, and other systems were so well coordinated that only a few post-construction field sketches were necessary. The overall MEP scope came in under budget, the approach cut nearly 10 weeks off the critical path, and the owner met the desired goal of beating its "historical best" timeline by three months – nearly 10 percent.

Maximizing the Benefits of BIM

Project owners must understand that BIM projects run differently. Clearly, BIM offers numerous benefits in terms of tighter control, shorter schedules, reduced risk, and higher return – particularly on complex projects with tight time frames. Ultimately, using BIM does not add cost to the project and the advantages can be significant. However, BIM works best when the owners have a clear vision of what they need the building to do and can convey system requirements, philosophy of operation, and goals of the facility.

Additionally, owners should be committed to making decisions earlier in the cycle than they might be accustomed to when taking a more conventional approach. The comprehensive nature of the information necessary to develop the 3D model supports better cost estimates and better scheduling, planning, management assists, clearer bid and less waste, but attaining these benefits requires a shift in the design/build process. BIM necessarily frontloads the project with more planning. It encourages owners to make decisions and answer questions earlier in the project. It also requires a collaborative atmosphere with smooth information flow. Unlike conventional design, BIM does not leave much room for "we'll figure that out later" – at least not if the owner wants to maximize the benefits of BIM.

Not all organizations are accustomed to this degree of pre-planning. The owner who will benefit the most is the one who has a firm grasp of the project scope going in and enough in-house talent to help define that scope for the designers. Owners should have a clear idea what they need for floor plans, layout, and functionality in terms of critical performance and compliance issues. Ideally, the owner also will have preselected vendors for process equipment and major systems so the facility design can be optimized around them. These goals can best be achieved when the owner's project team has enough decision-making authority to define the scope clearly during the planning phase. It is this discipline that enables the technology to generate complete construction drawings to solicit and obtain complete bids.

When circumstances limit or delay certain decisions, BIM can still offer advantages. BIM is flexible enough to accommodate indecision, but such delays result in a less complete, less well-defined model. Similarly, using BIM does not mean that designs are locked in stone or that changes can't ever be made. However, making changes after the shop drawings are generated can diminish some of the benefits of using BIM.

Due to these subtle shifts, when using BIM, it is always important to work with a company with good project management skills.

Selecting a Vendor/Partner

When considering BIM technology, it is important to remember that the benefits of using it are subject to the process, methodologies, and specifics of the project. To maximize the advantages of using BIM, project owners must select the right provider.

BIM is just a tool. In the hands of an inexperienced woodworker, the most sophisticated saw can still make bad cuts. BIM requires senior designers who have sufficient knowledge and experience of both the software applications and a deep understanding of the industry's unique needs as well as its design and constructability challenges. To use BIM successfully, the A/E professional must understand how the building needs to function and how it needs to be put together. He or she also must have access to or be able to design each of the highly specialized elements of a complex facility. That takes skill.

Training is a significant issue. Experienced, CAD-proficient designers who are familiar with construction processes can make the transition to BIM software more quickly than inexperienced personnel. Most of the software vendors offer multi-day training sessions, but becoming truly fluent in BIM can take months, even for senior designers, because BIM also requires a change workflow. In most cases, it makes sense to provide formal training to a small group of designers and allow them to gain experience by using BIM on a specific project. This cadre can then lead the BIM initiative and transfer their knowledge of the software and the processes to the rest of the organization over time. In addition, the firm may need to evaluate its information technology and infrastructure resources to optimize timely sharing of information among team members.

Concludes on page 56.

ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

PURE STEAM GENERATOR

DESIGN AND CONSTRUCTION OF PURIFIED WATER PACKAGES ♦ DOUBLE PASS REVERSE OSMOSIS ♦ R.O. + ELECTRODEIONIZATION HOT WATER SANITIZABLE ♦ ULTRAFILTRATION ♦ MULTIPLE - EFFECT DISTILLATION UNITS ♦ PURE STEAM GENERATORS ♦ STORAGE AND DISTRIBUTION LOOP ♦ COMPLETE TURN KEY PROJECTS ♦ VALIDATIONS IQ, OQ

www.elettracqua.com

The investment in high-level design talent and experience necessary to implement BIM ultimately benefits the project owners, because BIM also frees senior-level resources from the burden of overseeing draftspeople making manual changes to drawings and schedules so top design talent can spend more time doing what it does best. This is especially critical for highly complex projects, requiring the highest degree of design accuracy.

BIM requires the A/E firm to make a significant outlay in terms of both technology and personnel. Not all firms are equipped to make the necessary investment, which can run from well into five figures up to hundreds of thousands of dollars. To compensate for that investment, along with a reduction in billable hours, owners should expect a shift toward higher-cost hours or value-based fee structures for design and engineering.

Managing Risk

BIM technology is relatively new and few contracts have been written that speak to the respective responsibilities of the designer and the builder. Although risk assumption has always been a consideration, the advanced precision of the BIM model and the degree of data sharing that it involves raises some interesting issues. Current laws and legal precedents are based on clear boundaries between the designer and the builder. This is not the case with BIM. Just like when CAD was introduced 20 years ago and design/build a decade ago, BIM requires new legal contracts.

The American Institute of Architects (AIA) and Consensus DOCS have drafted several standardized contracts designed to allow all stakeholders to share the BIM project data. The documents from the two groups differ in how they address operations approaches, property insurance, additional liability coverage, and conflict resolution.

When using BIM, it is important to draft new contracts that clearly define responsibilities and apportion risk fairly. Whether starting with a standardized document or negotiating a contract from scratch, stakeholders will need to define the level of development required for each model element and determine authorized uses (i.e., analysis, cost estimating, scheduling, etc.) for the model and model elements. The contract should specify the party that will manage the model during each phase of the project. The document also should outline a protocol for addressing any conflicts or clashes that might arise in the model. Continued snags in interoperability between design disciplines can add to work flow drag and risk for sharing data. On the other hand, BIM can help minimize changes, errors, and omissions so it might reduce potential legal issues. Selecting a highly experienced BIM vendor can reduce implementation risks.

Conclusion

For owners and operators of complex facilities, BIM technology gives unprecedented control over challenging fast-track capital projects, expansions, or major renovations. During the planning phase and throughout construction, BIM provides a repository for information sharing and exchange among all stakeholders, and it also serves as a facility maintenance turnover tool. It increases accuracy and efficiency from design through purchasing and beyond, even to operator training and maintenance. In experienced hands, BIM can prove to be an exceptionally valuable project delivery tool that can help owners realize facility goals faster and more cost effectively.

References

1. American Institute of Architecture, "Building Information Modeling Protocol Exhibit," Document E202™, 2008.
2. Myers, J., "The Role of BIM in Green Design," http://www.greenbuildingcommunity.com/feature_full.php?cpfeatureid=31857&page=1, 17 November 2008 (accessed 20 November 2008).
3. Spatial Sustain, "General Motors Embraces BIM," http://www.vector1media.com, 14 February 2008 (accessed 1 December 2008).
4. Speed, V., "Strategies for Managing Risk in a New Era of Project Delivery," *Engineering News Record,* 31 March 2008, pp. L1-L4.
5. United States General Services Administration, GSA Building Information Modeling Guide Series 01 – Overview, 15 May 2007.
6. Figures 3a, 3b, and 3c, Integrated Project Services, Life Cycle Cost Analysis Report.

About the Authors

Andrew Signore, P.E., PMP, DBIA, CPIP is Co-Founder and CEO of Integrated Project Services (IPS), a full-service engineering, construction services, and compliance company. Throughout his 30 year career, he has conceived, designed, managed, and constructed a variety of manufacturing and support facilities. He is past Chairman of ISPE, past President of the ISPE Delaware Valley Chapter, and received ISPE's Distinguished Achievement Award for his many professional contributions to the Society. As an industry leader, Signore frequently lectures, publishes, and consults in areas of strategic planning, project management, and cGMP compliance. He can be contacted by telephone: +1-610-828-4090 or by email: asignore@ipsdb.com

Stephen R. Franey, RA has more than 14 years of diverse architectural and management experience. He designs and constructs a wide variety of manufacturing support and process facilities utilizing computer aided design technologies. By employing Building Information Modeling (BIM) technology to the design process, he provides 3D simulations in critical areas to limit material waste, shutdowns, and turnarounds for clients. He can be contacted by telephone: +1-610-828-4090 or by email: sfraney@ipsdb.com

Integrated Project Services (IPS), 2001 Joshua Rd., Lafayette Hill, Pennsylvania 19444, USA.

LEAN IN VALUE OUT

It's Common Knowledge at IPS

Chances are, you're already using lean practices in your production line. When it comes to capital projects, the knowledge leaders at IPS are at the forefront of Lean Project Delivery. Our team of subject matter experts and lean practitioners use Lean tools and techniques to craft innovative project delivery solutions than can dramatically reduce waste, improve operations, align with strategic business goals, and yield the maximum ROI.

To find more value in your next project – ***GO LEAN, GO IPS.***
Visit us at www.ipslean.com or contact Kimberly Goodman at 888.366.7660.

888.366.7660 | www.ipslean.com

ipslean

This article presents an innovative system for in-line process monitoring and control of freeze-drying pharmaceuticals in vials. This system is demonstrated to avoid drying failure in a wide range of operating conditions, as well as to minimize the duration of primary drying.

PAT Tools for the Optimization of the Freeze-Drying Process

by Davide Fissore, Roberto Pisano, Salvatore Velardi, Antonello Barresi, and Miquel Galan

Introduction

Freeze-drying is a process where water (or another solvent) is removed from a frozen product by sublimation. The process consists of three successive steps:

1. *Freezing*: the product to be dried is put over shelves in a chamber and its temperature is lowered so that the water (or the other solvent) is frozen. Unfortunately, not all the solvent freezes forming ice crystals, but a certain amount (sometimes significant) remains bonded to the product and must be finally desorbed. In some cases the product (the drug and the excipients) does not crystallize, but forms an amorphous glass which can retain a high amount of moisture.
2. *Primary drying*: the pressure of the chamber where the product is placed is reduced to a low value, thus causing ice sublimation. This process is carried out at very low temperatures (typically in the range -40°C to -10°C), but it requires energy that is generally supplied through the shelves.
3. *Secondary drying*: the amount of residual water, strongly bonded to the partially dried product, is reduced to a low value by using high vacuum and moderate temperatures, e.g., 20°C to 40°C. This step is required to ensure the long term preservation of the product.

Freeze-drying is widely used in the pharmaceutical industry because the low operating temperatures reduce the damages that can occur with traditional drying processes that use higher temperatures. Moreover, the freeze-dried product has a high surface area and can be easily re-hydrated. Finally, the high value of the pharmaceuticals allows for the use of a technology that can be quite expensive, because of the slow drying rate, the use of vacuum, and the high investment and operating costs. This technology has been used for many other products, including foodstuffs, because of some specific advantages that can be achieved.[1-6]

Despite the low operating temperatures, the product can be damaged even during a freeze-drying process as a consequence of a series of stresses that are applied to the molecules of the product, which can be rather labile, in the various stages of the process. Damages can occur during freezing, due to the large variation of solute concentration, of the ionic strength and eventually of pH – for which it is generally required to add cryoprotectants to the formulation. Moreover, product damages also can occur during drying. In regard to pharmaceutical products, the final appearance and reconstitution time can be strongly affected by processing. Because of the potential for damage, during primary drying the product temperature has to be carefully maintained below a limit value that is a characteristic of the product. In the case of solutes that crystallize during freezing, this maximum value corresponds to the eutectic point and product temperature has to be maintained below this value to avoid the formation of a liquid phase and the successive boiling due to the low pressure. In case of solutes that remain amorphous during freezing, the constraints are generally more demanding, as the maximum allowed product temperature is close to the glass transition temperature in order to avoid the collapse of the dried cake.[7] This value can be very low, lower than -30°C or -40°C in case of glucose, sucrose, and proteins, and is also dependent on the residual moisture. As a consequence, the constraints are active during or at the end of primary drying. The occurrence of the collapse of the dried cake, as well as of the shrinkage (that is generally due to limited and localized collapse phenomena), can be the cause of a higher residual water content

in the final product, a higher reconstitution time, and the loss of activity of the pharmaceutical principle. Furthermore, a collapsed product is often rejected because of its unattractive physical appearance.[8,9,10]

In addition to the temperature, the residual amount of frozen water has to be monitored in order to detect the ending point of primary drying. In fact, if secondary drying is started before the end of the previous step, the product temperature may exceed the maximum allowed value, thus causing melting or collapse, while if secondary drying is delayed, the cycle is not optimized and the cost of the operation increases.

Finally, the residual water content at the end of secondary drying has to be monitored. For most products, the target level of residual water is very low, usually from less than 1.0% to 3.0%, even if for certain products it has been demonstrated that a too low level of residual water should be avoided and the final residual moisture must be in a definite range.[11]

Therefore, it is clear that in order to manage a freeze-drying process, we need an efficient monitoring and control system, as it has been recently addressed in the Guidance for Industry Process Analytical Technology (PAT) issued by the US Food and Drug Administration in September 2004. This guidance describes a regulatory framework encouraging the design and implementation of innovative pharmaceutical development, manufacturing, and quality assurance to support innovation and efficiency to have safe, effective, and affordable medicines. PAT is considered to be a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. Quality cannot be tested into products, but it should be built-in or should be by design. The benefits that can be achieved by an optimal monitoring and control policy during a freeze-drying process have been recently discussed by Sadikoglu, et al.[12]

Monitoring of primary drying is particularly difficult as it is not possible to measure in-line the parameters of interest, i.e., the product temperature and the residual water content, without interfering with the process dynamics or impairing the sterile conditions usually required when pharmaceuticals are processed. An example of widespread, but invasive monitoring device is in fact, the measurement of the product temperature obtained by inserting a thin thermocouple (in lab-scale equipment) or a resistance thermal detector (in manufacturing) inside the vial. This may alter the elementary phenomena of nucleation and ice crystal growth. For example, the vials where thermocouples are placed tend to show a lower degree of supercooling than the surrounding vials and form fewer and larger ice crystals which results in lower product resistance to mass transfer and shorter drying time in comparison to the rest of the batch. Moreover, the insertion of thin thermocouples affects the heat transfer to the product. Finally, the probe insertion compromises the sterility of the product and it is not compatible with automatic loading/un-

Continued on page 60.

loading systems used in industrial-scale freeze-dryers, even if the last problem can be solved using a wireless system.

As a consequence of these technical limitations, even the most advanced industrial freeze-dryers have control systems that are no more than data acquisition tools for certain key variables and the freeze-drying cycle is usually specified by means of a recipe in terms of shelf temperature and chamber pressure over time. These values are obtained from an extended experimental campaign based on trials and errors. However, this procedure does not guarantee repeatable conditions for freezing and sublimation steps. There can be changes from batch-to-batch due to stochastic subcooling, leading to different nucleation temperatures. Moreover, there may be further changes over time introduced by the operator or caused by variations in the materials or operating conditions. In addition, the small-scale equipment, used for recipe development, and the large-scale equipment, used in the industrial process, are different with respect to vapor fluid-dynamics, temperature distribution over the shelves, heating/cooling capacity, and radiation effects. The result is that a recipe developed in a pilot-scale freeze-dryer could result in product damage when used in an industrial-size apparatus. Therefore, it is very important to have a system that can monitor the process and undertake adequate control actions to compensate for any changes in the operating conditions or in the performance of the equipment and to allow for a reliable scale-up from the pilot-scale to the industrial-scale unit.

In this framework, the authors have been involved with several European universities and pharmaceutical companies in a European research project (LYO-PRO) with the goal of optimizing and controlling the freeze-drying of pharmaceutical proteins. Presently, the research activity at Politecnico di Torino is focused on the design of monitoring systems that couple the hardware (physical sensor) with the software (mathematical model). When monitoring a process, this provides a method to estimate reliably those variables that cannot be measured (or whose measure is expensive or time consuming). When controlling a process, this provides a method to initiate a control action that considers the effects of it in the future; therefore, optimizing the process in addition to satisfying the constraints.

This article is focused on the primary drying phase of the freeze-drying process as this step is generally recognized to be the longest and the most risky phase of the whole process. This is due to the fact that the amount of bounded water in the partially dried product is higher during primary drying; therefore, the product has to be maintained below a very low temperature. If the temperature increases, collapse (or melting) can occur. As a consequence, the duration of primary drying can be very high. On the contrary, higher temperatures are allowed during secondary drying because of the lower amount of residual moisture. Monitoring and control of secondary drying will be the subject of a future work.

The state of the art of the techniques available to monitor primary drying have been recently reviewed and discussed by Barresi, et al.,[13] where an innovative and modular monitoring system is discussed, pointing out the advantages that can be obtained by means of redundancy and synergistic effect of various devices. This system also can provide information on both the whole batch and on single vials. The end of primary drying can be effectively determined through different techniques, allowing data reconciliation and resulting in a very robust system. The measurement of product temperature and residual water content is not possible with "classical" monitoring tools, e.g., thermocouples. In order to use modern control tools that allow for process optimization and guarantee product quality, other parameters, e.g., the heat transfer coefficient between the shelf and the vials and the resistance of the dried product to vapor flow, have to be known. These variables can hardly be directly measured, but they can be estimated: a simple approach consists of perturbing the system and solving the appropriate dynamical model by fitting it to the experimental physical response to recover the unknown parameters. A well known example of this approach is the Pressure Rise Test (PRT). This article proposes an innovative algorithm, called *Dynamic Parameters Estimation* (DPE), based on the unsteady-state mass and heat balances for the product in the vials. A new predictive approach to the control is also presented, illustrating the performance of a control system developed by the authors. Results obtained in a small industrial-type apparatus (LyoBeta 25 by Telstar, Spain) with a chamber volume of 0.2 m^3 and equipped with this control software are shown to prove the effectiveness of the proposed algorithms in a wide range of operating conditions, thus, demonstrating that product damages can be avoided even when the process becomes mass-transfer controlled and when the operating pressure is suddenly changed.

Process Monitoring: DPE Algorithm

Non-invasive monitoring techniques have been proposed in the past. Most of these techniques use the in-line measure of the pressure rise occurring when the valve placed between the drying chamber and the condenser is closed for a short time (typically from five to 30 seconds) and estimate the temperature of the sublimating interface and other parameters, using a mathematical model of the process. Several algorithms were proposed in the past to interpret the PRT, namely the Barometric Temperature Measurement,[4,5,14] the Manometric Temperature Measurement,[15-18] the Dynamic Pressure Rise,[19] and the Pressure Rise Analysis.[20-22] What differentiates one method from the others is the type and the detail of the mathematical model used and the parameters that are estimated. In fact, some of the previous approaches are based on the sum of elementary mechanisms or rely on simplifications. The sublimation flux of the solvent can be calculated from the same mathematical model used to fit the curve of pressure rise or from the slope of the curve of pressure rise at the beginning of the test: the two procedures give of course similar results and this can be used as a consistency check. By performing some PRTs throughout primary drying, it is possible to evaluate the evolution of the product temperature, and by integrating the solvent flux, it is possible to calculate the residual ice content of the solid, thus, detecting the ending point of the primary drying.

The *Dynamic Parameters Estimation* (DPE) algorithm is an advanced tool proposed by Velardi, et al.,[13,23] to interpret the results of the PRT in a more reliable way: it implements an unsteady-state model for mass transfer in the drying chamber and heat transfer in the product, given by a set of partial differential equations describing:

- conduction and accumulation of heat in the frozen layer of the product
- mass accumulation in the drying chamber during the PRT
- time evolution of product thickness

The details of the model can be found in Velardi, et al.,[23] and in Barresi, et al.,[13] and are summarized in Annex 1. The system of equations is integrated in time in the internal loop of a curvilinear regression analysis: the cost function to minimize in a least square sense is the difference between the simulated values of the pressure in the drying chamber and the actual values measured during the PRT. The parameters that are estimated are the temperature of the sublimating interface at the beginning of the PRT and the mass transfer resistance to vapor flow in the dried layer. Beside these, other results are available:

- the temperature profile of the product at any axial position (and thus at the product bottom) at each time during the PRT
- the heat transfer coefficient between the heating shelf and the vial
- the actual thickness of the frozen portion of the product
- the solvent sublimation flux in the drying chamber
- the estimation of the time required to complete primary drying

These measurements are not made continuously, but on a timely basis, typically every 30 to 60 minutes. An example of the results that can be obtained when the DPE algorithm is used to monitor a freeze-drying cycle as shown in Figure 1. It is possible to see that in the first part of the cycle the temperature at the bottom of the vials estimated by means of the DPE algorithm is very close to the value measured by a thermocouple placed in a vial. The earlier increase of the temperature measured by the thermocouple is due to the fact that the sublimation rate is generally higher in the monitored vial with respect to the other vials of the batch; therefore, the primary drying is completed early. The ratio of the signals of a capacitance manometer and of a thermal conductivity gauge, like the Pirani gauge, is used to asses the end of primary drying. At that point, the concentration of water into the drying chamber becomes very low; thus, the pressure measured by Pirani (that is generally calibrated for air) approaches that measured by the capacitive gauge.[24] This method has been used in this case to verify independently the end of primary drying, even if the Pirani gauge is not generally used in production

Continued on page 62.

plants because it suffers steam sterilization. New models of the Pirani gauge, using nickel or platinum for the filament rather than the standard tungsten, can cope with several sterilization cycles.

The estimated product temperature decreases nearby the end-point: similar results also have been obtained with the other algorithms based on the PRT. One of the proposed causes to explain this is that when primary drying is approaching the end, a fraction of the vials (mainly the edge-vials, because of radiation from the chamber walls) has already finished sublimating, while DPE continues interpreting pressure rise curves assuming batch uniformity or rather a constant number of sublimating vials. A decrease in pressure rise, corresponding to a lower sublimation rate, may be interpreted by the algorithm as a reduction of the front temperature. As a consequence, the monitoring methods based on the PRT cannot be used in the last part of primary drying. The DPE algorithm is based on a much more detailed model of the drying; the result is that the estimations can be consistent for a large fraction of the primary drying. Moreover, the DPE algorithm could be modified in order to take into account in some way the batch heterogeneity.[25] In any case, care must be given when information obtained using monitoring methods based on the PRT is used to control the process. In fact, all these algorithms estimate the mean value of the product temperature, but in some vials (e.g., those placed at the edges of the tray) product temperature can be higher. This has to be taken into account when setting the target temperature in order to avoid drying failure in those vials; this issue will be addressed in the following discussion.

Process Control

The control system for a freeze-drying process should guar-

Annex 1. DPE Algorithm

During the PRT heat transfer in the frozen layer is described by the following equations:

$$\frac{\partial T}{\partial t} = \frac{k_f}{\rho_f c_{p,f}} \frac{\partial^2 T}{\partial z^2} \quad \text{for } t > t_0,\ 0 \le z \le L_f \tag{A1}$$

$$T\big|_{t=0} = T_{i0} + \frac{z}{k_f} \Delta H_s \left(\frac{k_1 M_w}{R T_{i0}}\right)\left(\frac{p_{w,i0} - p_{w,c0}}{L - L_f}\right) \quad \text{for } 0 \le z \le L_f \tag{A2}$$

$$k_f \left.\frac{\partial T}{\partial z}\right|_{z=0} = \Delta H_s \left(\frac{k_1 M_w}{R T_i}\right)\left(\frac{p_{w,i} - p_{w,c}}{L - L_f}\right) \quad \text{for } t \ge t_0 \tag{A3}$$

$$k_f \left.\frac{\partial T}{\partial z}\right|_{z=L_f} = K_v (T_{fluid} - T_B) \quad \text{for } t \ge t_0 \tag{A4}$$

Thermodynamic equilibrium is assumed at the sublimating front, corresponding to the axial position $z = 0$. The heat fluxes at $z = 0$ and at $z = L_f$, corresponding to the internal bottom of the vial, are generally not equal during the PRT, because of accumulation in the frozen layer, except at the beginning because of the pseudo-stationary hypothesis. Thanks to this assumption, the expression for the heat transfer coefficient, K_v, assumed constant during the PRT, can be derived by equating the boundary conditions (A3) and (A4), both taken at $t = t_0$. Thus:

$$k_f = \left[\frac{T_{fluid} - T_{i0}}{\Delta H_s \left(\frac{k_1 M_w}{R T_{i0}}\right)\left(\frac{p_{w,i0} - p_{w,c0}}{L - L_f}\right)} - \frac{L_f}{k_f}\right]^{-1} \tag{A5}$$

The previous equations are completed with the equation providing the dynamics of the water vapor pressure rise in the chamber, which consists in the material balance for the vapor flowing into the chamber environment. Applying the ideal gas law and rewriting the mass flow rates as functions of the pressure driving force between the interface and the chamber, it follows:

$$\left(\frac{M_w V_c}{R T_c}\right) \cdot \frac{dp_{w,c}}{dt} = N_v A \frac{k_1 M_w}{R T_i} \frac{p_{w,i} - p_{w,c}}{L - L_f} \tag{A6}$$

Finally the total pressure can be calculated taking into account a constant leakage in the chamber:

$$P_c = p_w + p_{in} = p_w + F_{leak} t + P_{in0} \quad \text{for } t \ge t_0 \tag{A7}$$

$$P_w\big|_{t=0} = p_{c0} - P_{in0} \quad \text{for } t = t_0 \tag{A8}$$

If the value of the chamber temperature T_c is not available, it can be substituted with the product temperature at the interface of sublimation, usually committing a small error.

The actual thickness of the frozen layer is determined through a material balance written across the moving interface, which is solved contemporaneously to the previous equations. The water vapor flow rate at the interface is equal to the difference between the rate of disappearance of the frozen mass and the rate of formation of the dried mass, according to the following equation:

$$\dot{m}_w = N_v \left(\rho_f A \frac{dL_f}{dt} - \rho_d A \frac{dL_f}{dt}\right) \tag{A9}$$

The material balance at the interface can be integrated in time between the previous PRT and the actual one, obtaining:

$$L_f = L_f^{(-1)} - \frac{M_w}{R \Delta\rho} \int_{t_0^{(-1)}}^{t_0} \left(\frac{k_1}{T_i} \frac{p_{w,i} - p_{w,c}}{L - L_f}\right) dt \tag{A10}$$

where $\Delta\rho = \rho_f - \rho_d$, and the superscript "(-1)" refers to quantities calculated or measured in the previous PRT. The integral on the right hand side can be solved applying the trapezoidal rule of integration:

$$L_f = L_f^{(-1)} - \frac{M_w}{R \Delta\rho} \left[\left(\frac{k_1}{T_{i0}} \frac{p_{w,i0} - p_{w,c0}}{L - L_f}\right) + \left(\frac{k_1^{(-1)}}{T_{i0}^{(-1)}} \frac{p_{w,i0}^{(-1)} - p_{w,c0}^{(-1)}}{L - L_f^{(-1)}}\right)\right] \cdot \frac{t_0 - t_0^{(-1)}}{2} \tag{A11}$$

antee product quality, in addition to minimizing the drying time. Various approaches have been proposed in the past to get these results; most are based on the use of a mathematical model of the process that is used to calculate off-line the optimal operating conditions, i.e., the shelf temperature and the chamber pressure to minimize the duration of the primary drying. No feedback from the real operation was available and so these control systems were not able to modify the operating conditions to compensate for unpredicted changes in the operating conditions.[26-31] Moreover, this approach requires that the model perfectly describes the dynamics of the process and that all the parameters and all the variables of the process are known; the inadequacy of the model or a different value of some parameters can result in a more or less serious failure. In addition, there are other causes of batch failure. A typical case is when freeze-drying is conducted with a loading different from usual or in a "similar" equipment. If the recipe is just a sequence of set points, calculated off-line, for the operating parameters of the freeze-dryer, the state of the product is not taken into account, and due to different heat fluxes or to the effect of a different hydrodynamics and pressure distribution in the chamber, failure can occur in some cases. Finally, some unexpected variation of the parameters set-point (e.g., pressure) can damage or at least endanger the product. Failure occurs if the recipe is not "robust enough," that is if the design space is not wide enough that the system remains inside it. The solution to the problem is a good control system that can

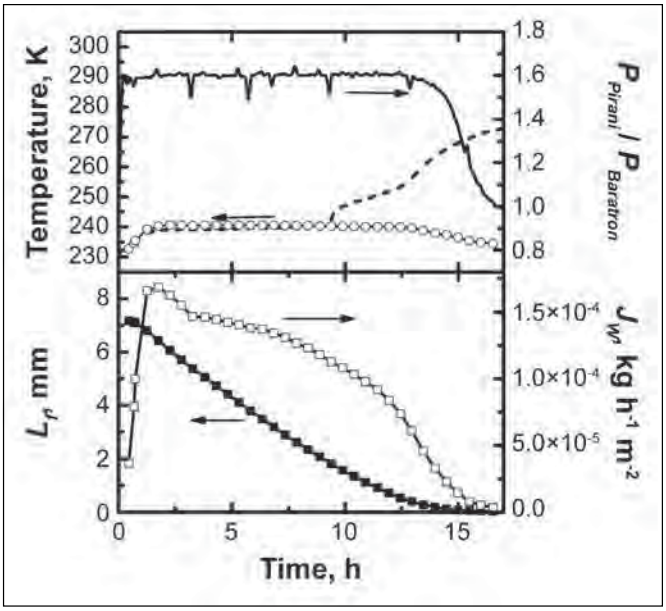


Figure 1. Example of results obtained when the DPE algorithm is used to monitor a freeze-drying cycle. Data refers to the freeze-drying of a 10% w/w sucrose aqueous solution (T_{shelf} = 265 K, P_c = 10 Pa, $d_{v,i}$ = 14.2·10^{-3} m, N_v = 175, L = 7.21·10^{-3} m). Upper graph: ratio of the pressure signals given by the Pirani and Baratron gauges (solid line), product temperature measured at the bottom of a vial (dashed line) and estimated by DPE algorithm (symbols). Lower graph: thickness of the frozen layer and sublimation flux.

Continued on page 64.

compensate for disturbances and changes in the set-up and that uses some in-line process measurements.

Some already commercially available systems use the PRT as a sensing device, e.g., Oetjen and coworkers proposed to use the results of the Barometric Temperature Measurement and a set of heuristics for the calculation of the control actions.[4,5] The use of the Manometric Temperature Measurement in a control algorithm that manipulates the shelf temperature and the chamber pressure also has been proposed and demonstrated to be a useful tool for development of a lyophilization cycle during a single freeze-drying run, but it has no predictive capacity and it cannot be used to perform a true process optimization.[32-34]

Barresi, et al.,[13,35,36] proposed to use the DPE algorithm in a control loop where the heating fluid temperature is the manipulated variable - *Figure 2*. This control algorithm uses the estimations of the product temperature, the effective heat transfer between the heating fluid and the product at the bottom of the vial, the diffusivity coefficient of the vapor in the dried layer obtained by means of DPE, some process variables (i.e., the temperature of the fluid, the pressure in the chamber, and the cooling rate of the freeze-dryer), and a simplified mathematical model for primary drying.[31] In order to run the control algorithm, the prediction horizon, which is the time throughout the algorithm estimates the evolution of the product

Annex 2. Control Algorithms

The control algorithm uses an unsteady-state model of the process which supplies the evolution of both product temperature and frozen layer thickness. The ice front position is described by Equation A12:

$$\frac{dL_f}{dt} = -\frac{1}{R_P\,(\rho_f - \rho_d)}\,(p_{w,i} - p_{w,c}) \qquad \text{(A12)}$$

The mass transfer resistance (R_p) can be calculated from the effective diffusivity of vapor in the dried layer (k_1), which can be estimated by DPE, using Equation A13:

$$R_p = \frac{RT_i}{M_w} \cdot \frac{L - L_f}{k_1} \qquad \text{(A13)}$$

Assuming pseudo-steady conditions into the frozen layer, the following relationship between L_f and the front temperature (T_i) is obtained:

$$\left(\frac{1}{K_v} + \frac{L_f}{k_f}\right)^{-1}(T_{fluid} - T_i) = \frac{\Delta H_s M_w}{RT_i}\,\frac{k_1}{L - L_f}\,(p_{w,i} - p_{w,c}) \qquad \text{(A14)}$$

The algebraic Equation A15, instead, results from the integration of the energy balance into the frozen layer and relates the interface temperature and position to the temperature at the bottom of the vial:

$$T_B = T_{fluid} - \left(\frac{1}{K_v} + \frac{L_f}{k_f}\right)^{-1}(T_{fluid} - T_i) \qquad \text{(A15)}$$

Previous equations are integrated along the prediction horizon, i.e., from the initial time (t_0) up to the horizon time (t_N) set by the User or to the time corresponding to the end of the drying (t_{N^*}); t_0 is zero at the first test and equal to the elapsed time from the first test in next runs.

If a feedback algorithm is used, the optimal heating strategy is calculated throughout the prediction horizon considering the optimal sequence of set-points of the fluid temperature as a piecewise-linear function as shown in Equation A16:

$$\begin{aligned}
&t_0 \le t < t_1 \;\rightarrow\; T_{fluid,sp,1} = T_{fluid}\,(t_0) + K_P(T_B(t_0) - T_{target})\\
&t_1 \le t < t_2 \;\rightarrow\; T_{fluid,sp,2} = T_{fluid}\,(t_1) + K_P(T_B(t_1) - T_{target})\\
&\vdots\\
&t_{N-1} \le t < t_N \;\rightarrow\; T_{fluid,sp,N} = T_{fluid}\,(t_{N-1}) + K_P(T_B(t_{N-1}) - T_{target})
\end{aligned} \qquad \text{(A16)}$$

where K_P is the proportional gain of the controller and the target temperature (T_{target}) is initially assumed equal to the maximum temperature allowed by the product (T_{max}). The design of the controller consists of determining its optimal gain according to the criterion of minimization of a particular cost function, that in this case corresponds to the Integral Square Error (ISE) as shown in Equation A17:

$$\min_{K_P}(\text{ISE}) = \min_{K_P}\int_{t_0}^{t_N}(T_B(t) - T_{target})^2 dt \qquad \text{(A17)}$$

T_B is the product temperature at the bottom of the vial and its evolution is calculated using the previous mathematical model (see Equations A12 to A15) integrated throughout the prediction horizon. It must be highlighted that the solution of Equation A17, i.e., the design of the controller, does not guarantee that product temperature remains below T_{max} because to obtain that result a constrained optimization, that is much less robust, would have been required. As a consequence, the evolution of T_B vs. time as a function of the heating policy given by the controller is evaluated (along the prediction horizon) and the possible overshoot $T_{B,max} - T_{max}$ is calculated: if this overshoot exists, then the design of the controller is repeated, assuming a lower target temperature, given by T_{max} diminished by the overshoot.

If a model-based algorithm is used, the optimal heating strategy throughout the prediction horizon is calculated as a piecewise-linear function in such a way that the bottom product temperature is maintained equal to its target. The control algorithm uses the previously described model of the process to calculate the fluid temperature needed to drive T_B to its target as faster as possible:

$$\begin{aligned}
&t_0 \le t < t_1 \;\rightarrow\; T_{fluid,sp,1} = T_{target} + (T_{target} - T_i(t_0))\left[K_v\left(\frac{1}{K_v} + \frac{L_f(t_0)}{k_f}\right) - 1\right]^{-1}\\
&t_1 \le t < t_2 \;\rightarrow\; T_{fluid,sp,2} = T_{target} + (T_{target} - T_i(t_1))\left[K_v\left(\frac{1}{K_v} + \frac{L_f(t_1)}{k_f}\right) - 1\right]^{-1}\\
&\vdots\\
&t_{N-1} \le t < t_N \;\rightarrow\; T_{fluid,sp,N} = T_{target} + (T_{target} - T_i(t_{N-1}))\left[K_v\left(\frac{1}{K_v} + \frac{L_f(t_{N-1})}{k_f}\right) - 1\right]^{-1}
\end{aligned} \qquad \text{(A18)}$$

The same considerations about the target temperature used by the feedback algorithm can be extended to the model-based controller.

temperature and computes a proper heating policy, and the control horizon, which is the time between a control action and the next one, must be set. After that, the algorithm calculates a sequence of suitable set-points for the fluid temperature ($T_{fluid,sp}$), one for each control interval along the prediction horizon, in such a way that the product temperature is as close as possible to its target. At the beginning of primary drying, when the temperature of the product is well below the upper limit, the heating fluid temperature is raised at its maximum rate compatible with the actual capacity of the equipment, and by this way, the product approaches its limit as fast as possible. After this first step, a PRT is performed and the software, using DPE algorithm, estimates the product temperature at the bottom of the vial (where the temperature is higher) over all the prediction horizon and calculates again the optimal heating policy according to the current system state. This is regularly repeated at each successive PRT so that potential mismatches between the model predictions and the actual process behavior can be taken into account. If the estimated product temperature would approach its limit, the shelf temperature is reduced in such a way that the product is maintained below its target, thus, preserving the integrity of the product.

Two control systems based on a feedback and on a model-based algorithm have been proposed and compared.[37] Annex 2 gives the details of the mathematical model used by the control algorithm. The feedback controller calculates the control action, i.e., the set-point for the temperature of the heating fluid, as a function of the difference between the bottom product temperature and the maximum allowed value. The gain of this controller is calculated in such a way that the difference between product temperature and the target value is minimized along the prediction horizon; to this purpose, a mathematical model is required to calculate the evolution of the product temperature as a function of the temperature of the heating fluid.[31] The model-based algorithm calculates

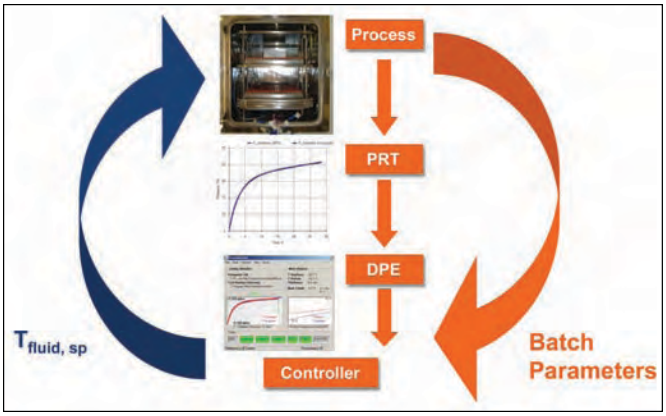


Figure 2. Operating principle of a control loop using DPE algorithm as state-estimator tool. The chamber of the equipment used for the experiments (modified LyoBeta 25 by Telstar), an example of the fitting of the PRT and a screen-plot of the parameters supplied by the system (that can be used also in simple monitoring modality) are shown.

Continued on page 66.

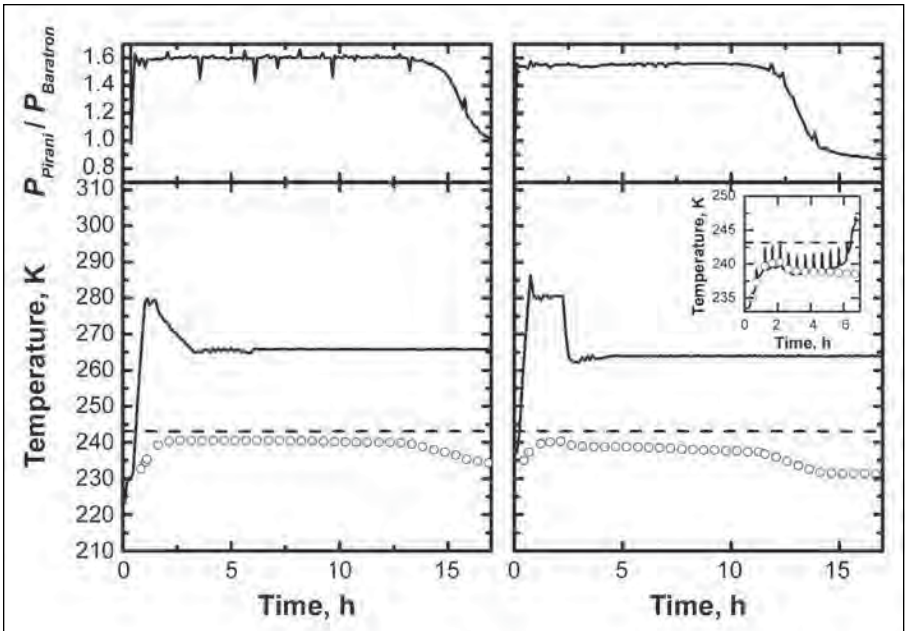


Figure 3. Examples of the application of the control algorithm to the freeze drying process of a 10% solution of sucrose ($d_{v,i}$ = 14.2•10^{-3} m, L = 7.2•10^{-3} m, P_c = 10 Pa). Results obtained using the feedback controller are shown in the left hand graph (N_v = 175), while results obtained using the model-based controller are shown in the right hand graph (N_v = 205). Upper graphs: ratio of the pressure signals given by the Pirani and Baratron gauges. Lower graphs: shelf temperature (solid line), maximum product temperature estimated by DPE (symbols) and limit temperature (-30°C, dashed line); the product temperature measured by a thermocouple is shown in the upper part of the graph on the right.

the set-point fluid temperature using the model of Velardi and Barresi[31] and imposing that the temperature of the product at the bottom of the vial is equal to the target value. The set-point of T_B is generally lower than the target temperature set by the user, corresponding to the maximum value allowed by the product, because the controller iteratively calculates a new target in order to avoid any temperature overshoot, thus, guaranteeing that product temperature is always maintained below the maximum allowed value. Moreover, the set-point of T_B is calculated taking also into account temperature rises caused by PRT. Both control algorithms take into account the actual thermal dynamics of the freeze-dryer, i.e., the actual cooling and heating rates.

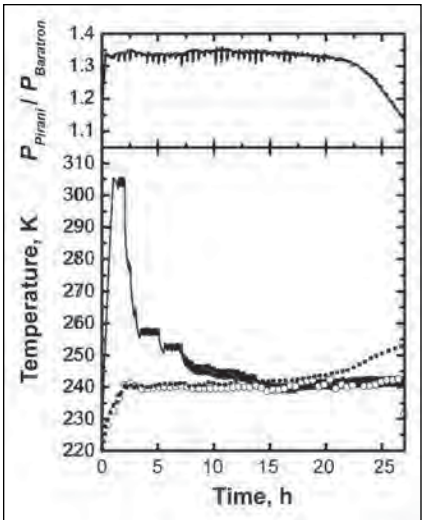


Figure 4. Example of an optimal freeze-drying cycle obtained using the model-based controller to set the fluid temperature for the freeze drying of a formulation containing 4% w/w mannitol, 1% w/w sucrose and excipients (L = 5•10^{-3} m, N_v = 132, P_c: 10 Pa, maximum allowed temperature = 240 K). Upper graph: ratio of the pressure signals given by the Pirani and Baratron gauges. Lower graph: fluid temperature (solid line), product temperature at bottom of the vial estimated by DPE (symbol) and measured through a thermocouple (dotted line).

Figure 3 shows two examples of the results that can be obtained when this control algorithm is used to control the process: the ice temperature at the bottom of the vial estimated by DPE algorithm is shown, as well as the value of the temperature of the heating fluid in case of feedback algorithm (on the left) and of model-based algorithm (on the right). It can be observed that the estimated maximum product temperature never overcomes the limit value that has been fixed, and the maximum allowable heating rate is obtained throughout all primary drying, thus, minimizing the duration of this step. The product temperature rise during a PRT is taken into account in calculating the heating policy. As a consequence, the value of the product temperature is slightly lower than the set-point, and the product temperature never overcome its limit, not even during the PRT, as it is shown by the temperature measurement given by a thermocouple placed in correspondence of the bottom of a vial. The drying time resulting when the model-based algorithm is used is slightly higher than that obtained by the feedback algorithm, but the simpler mathematical formulation (since no optimization is involved in the calculation) and the smaller computation time make the model-based approach more suitable for in-line control. It can be noted that, as discussed above, when primary drying is approaching the end, the product temperature estimated by means of

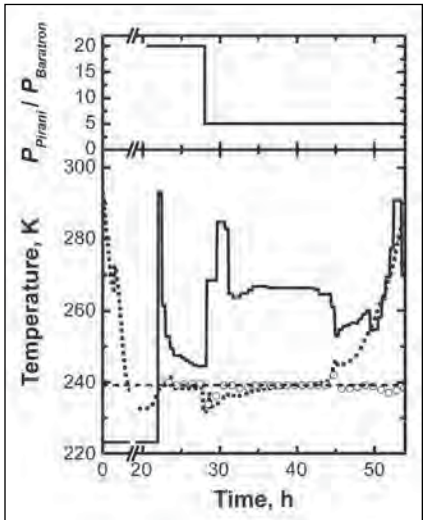


Figure 5. Example of the results obtained during a freeze-drying cycle run using the control algorithm for the primary drying stage. The batch is composed of shielded glass vials on tray (N_v = 155, L = 9.9•10^{-3} m, $d_{v,i}$ = 20.8•10^{-3} m) filled with 3 mL of a 10% w/w sucrose aqueous solution. After freezing, the chamber pressure has been set at 20 Pa and then lowered to 5 Pa after about 5 h (upper graph). The maximum allowable product temperature has been set to 240 K. The time evolution of the shelf temperature (solid line), and of the temperature at the bottom of the vials estimated using DPE algorithm (symbol) and measured by a thermocouple (dotted line) is shown in the lower graph.

DPE algorithm decreases; this behavior must be taken into account when setting the parameters of the control algorithm and in the last part of the cycle it is advisable to use the sequence of control action suggested in the previous steps, without updating it on the basis of the new (misleading) measurements. The same problem was evidenced also by Gieseler, et al.,[34] when using a different control algorithm. Oetjen and Haseley[14] proposed to use the decrease in the estimated interface temperature as an indication of end of sublimation; in any case, the end of primary drying could be reasonably estimated by extrapolating the predictions of the interface position obtained using DPE in the initial part of the run.

In both examples of Figure 3, the heat transfer from the shelf controlled the sublimation rate and the fluid temperature was usually maintained almost constant in the second part of the drying: the value of the shelf temperature assured the maximum sublimation rate since it was significantly greater than the product temperature and chamber pressure was not very influent.

In some cases, the vapor transport through the solid matrix controls the drying rate. Transition to mass transfer control may occur as a consequence of the increase of dry cake thickness, the formation of a crust, or the increase of the cake resistance during the process due to a change in its structure. There is a strong risk of failure because if the heat flux is not properly reduced, the product temperature increases. Moreover, it is very difficult to predict the occurrence of such transition. The proposed control algorithm can be effective also in this case since it guarantees the product integrity and the maximum flow rate at the operating pressure. Figure 4 shows the results obtained in a cycle where the process becomes mass-transfer controlled (after about 15 hours), as it is confirmed by the analysis of the transport coefficients estimated by the DPE algorithm. It can be observed that the fluid temperature calculated by the controller approaches the product temperature: the driving force for the heat transfer becomes very small because the constraint on the maximum temperature of the product is effective and the controller indicates that, at this moment, a reduction in the chamber pressure is convenient to increase the sublimation rate. In this case, DPE demonstrates good results up to the end of primary drying and the product temperature estimated agrees with thermocouple measurements, at least until the monitored vials are representative of the entire batch. Of course an in-line change of the chamber pressure might be useful to reduce the drying time, restoring heat transfer control.[38] Figure 5 shows the results obtained when a cycle is controlled using the previously described control algorithm and chamber pressure is changed in order to minimize the drying time when the process was approaching mass-transfer control. It is important to observe that when the pressure is decreased, the controller calculates a higher set-point for the temperature

Continued on page 68.

of the heating fluid. The result is that the temperature is maintained always close to the limit value that was previously set and the difference between the temperature of the fluid and that of the product is higher with respect to the value obtained before the pressure change. This means that the heat flux from the fluid to the product is higher, thus, resulting in a shorter drying time.

Conclusions and Future Perspectives

Results that can be obtained when a vial freeze-drying process is monitored and controlled using a new control algorithm have been shown and discussed in the article. The unique key features of this control system have been highlighted and are briefly listed below:

- uses a simple mathematical model of the drying process in order to calculate the optimal values of the shelf temperature that guarantee product quality and minimize the drying time
- uses the estimates of the state of the system and of the process parameters that are available by interpreting the PRT with the DPE algorithm and after each control time, a new DPE test is carried out and a new sequence of control actions is calculated, thus, compensating for model deviations and process disturbances
- considers the actual heating/cooling capacity of the freeze-dryer
- predicts potentially damaging temperature overshoots and anticipates accordingly the control actions
- considers temperature rises caused by PRT

Product failures can be avoided, even when the process becomes mass-transfer controlled or when the pressure in the chamber is varied. This tool appears to be an effective and efficient solution for process control in production plants, at least at relatively small scale, when it can be possible to periodically close the valve quickly. The system can be very effective also for pilot-scale units used for the initial R&D stage and it can make the passage from R&D to production scale very straightforward. To this purpose, the proposed control algorithm has been successfully tested in a pilot-scale freeze-dryer.

Further improvements can be done in the monitoring and control algorithm: in fact, control actions calculated by the algorithm are a function of some parameters (e.g., the cake resistance and the overall heat transfer coefficient between the heating/cooling fluid and the product) that can be variables among the vials of the batch. Heterogeneity of the batch is caused by radiation from chamber walls, shelves and door, the fluid-dynamics of the water vapor in the drying chamber, non-uniform temperature of the heating shelf, and non-uniform initial filling height.[39] If an aggressive control policy, based on the estimation of the "mean" state of the batch is used, a fraction of the product, whose temperature is higher, can be damaged or there can be a fraction of vials that does not satisfy the requirements because of batch heterogeneity. Thus, the control system has to cope with this occurrence. It could be possible to modify the DPE algorithm in order to take into account the variance of temperature (and of other parameters) of the batch; preliminary results have shown that this may present some difficulties.[25] Another approach consists of using the information coming from temperature measurement, coupled to a soft-sensor, in several vials.[36] Work is in progress to develop a new monitoring system that can be coupled with the control algorithm that does not require to close the valve in the spool, and this can be used in very large industrial equipment.

List of Symbols

A	cross surface of the vial, m^2
$c_{p,f}$	specific heat of the frozen layer, J $kg^{-1}K^{-1}$
$d_{v,i}$	inner diameter of the vial, m
F_{leak}	leakage rate, Pa s^{-1}
ΔHs	heat of sublimation, J kg-1
J_w	sublimation flux, kg h^{-1} m^{-2}
K_p	gain of the proportional controller
K_v	overall heat transfer coefficient, J m^{-2} s^{-1} K^{-1}
k_1	effective diffusivity of vapor in the dried layer, m^2 s^{-1}
k_f	thermal conductivity of the frozen product, J m^{-1} s^{-1} K^{-1}
L	product thickness after freezing, m
L_f	thickness of the frozen layer, m
M	molecular weight, kg $kmol^{-1}$
m	mass flow rate, kg s^{-1}
N_v	number of vials of the batch
p	partial pressure, Pa
P	total pressure, Pa
R	ideal gas constant, J $kmol^{-1}$ K^{-1}
R_p	mass transfer resistance to vapor flow in the dried layer, m s^{-1}
T	temperature, K
t	time, s
V	volume, m^3
z	axial coordinate, m

Greeks

ρ_d	effective density of the dried layer, kg m^{-3}
ρ_f	effective density of the frozen layer, kg m^{-3}

Subscripts and Superscripts

0	value at t = 0, initial time for the interval considered
(-1)	PRT before the actual one
B	vial bottom, corresponding to $z = L$
c	drying chamber
fluid	heating fluid
i	sublimating interface, corresponding to z = 0
in	inert gas
max	maximum value
shelf	heating shelf
sp	set-point
target	target value
w	water vapor

Abbreviations

DPE	Dynamic Parameters Estimation
PRT	Pressure Rise Test

References

1. Mellor, J.D., **Fundamentals of Freeze-Drying,** London: Academic Press, 1978.
2. Liapis, A.I., **Freeze Drying. Handbook of Industrial Drying** (edited by A.S. Mujumdar), Chapter 9, New York: Marcel Dekker Inc., 1987.
3. Jennings, T.A., **Lyophilization: Introduction and Basic Principles,** Boca Raton: Interpharm/CRC Press, 1999.
4. Oetjen, G.W., **Freeze-Drying,** Weinheim: Wiley-VCH, 1999.
5. Oetjen, G.W., Haseley, P., **Freeze-Drying,** 2nd Edition, Weinheim: Wiely-VHC, 2004.
6. Rey, L., May, J.C., **Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products,** New York: Marcel Dekker Inc., 2004.
7. Franks, F., **Freeze-Drying of Pharmaceuticals and Biopharmaceuticals,** Cambridge: Royal Society of Chemistry, 2007.
8. Pikal, M.J., Shah, S., "The Collapse Temperature in Freeze Drying: Dependence on Measurement Methodology and Rate of Water Removal from the Glassy Phase," *International Journal of Pharmaceutics*, Vol. 62, 1990, pp. 165-186.
9. Wang, W., "Lyophilization and Development of Solid Protein Pharmaceuticals," *International Journal of Pharmaceutics,* Vol. 203, 2000, pp. 1-60.
10. Rambhatla, S., Obert, J.P., Luthra, S., Bhugra, C., Pikal, M.J., "Cake Shrinkage during Freeze Drying: A Combined Experimental and Theoretical Study," *Pharmaceutical Development and Technology,* Vol. 1, 2005, pp. 33-40.
11. Hsu, C.C., Ward, C.A., Pearlman, R., Nguyen, H.M., Yeung, D.A., Curley, J.G., "Determining the Optimum Residual Moisture in Lyophilized Protein Pharmaceuticals," *Developments in Biological Standardization,* Vol. 74, 1992, pp. 255-271.
12. Sadikoglu, H., Ozdemir, M., Seker, M., "Freeze-Drying of Pharmaceutical Products: Research and Development Needs," *Drying Technology,* Vol. 24, 2006, pp. 849-861.
13. Barresi A.A., Pisano, R., Fissore, D. Rasetto, V., Velardi, S.A., Vallan, A., Parvis, M., Galan, M., "Monitoring of the Primary Drying of a Lyophilization Process in Vials," *Chemical Engineering and Processing,* Vol. 48, 2009, pp. 408-423.
14. Oetjen, G.W., Haseley, P., Klutsch, H., Leineweber, M., "Method for Controlling a Freeze-Drying Process," United States Patent n. 6,163,979 A1.
15. Milton, N., Pikal, M.J., Roy, M.L., Nail, S.L., "Evaluation of Manometric Temperature Measurement as a Method of Monitoring Product Temperature during Lyophilisation," *PDA Journal of Pharmaceutical Sciences,* Vol. 5, 1997, pp. 7-16.
16. Tang, X.C., Nail, S.L., Pikal, M.J., "Evaluation of Manometric Temperature Measurement, A Process Analytical Technology Tool for Freeze-Drying: Part I, Product Temperature Measurement," *AAPS Pharmaceutical Science and Technology,* Vol. 7, No. 1, 2006, article 14.
17. Tang, X.C., Nail, S.L., Pikal, M.J., "Evaluation of Manometric Temperature Measurement, A Process Analytical Technology Tool for Freeze-Drying: Part II, Measurement of Dry Layer Resistance," *AAPS Pharmaceutical Science and Technology*, Vol. 7, No. 4, 2006, article 93.
18. Tang, X.C., Nail, S.L., Pikal, M.J., "Evaluation of Manometric Temperature Measurement (MTM), A Process Analytical Technology Tool in Freeze Drying: Part III, Heat and Mass Transfer Measurement," *AAPS Pharmaceutical Science and Technology,* Vol. 7, No. 4, 2006, article 97.
19. Liapis, A.I., Sadikoglu, H., "Dynamic Pressure Rise in the Drying Chamber as a Remote Sensing Method for Monitoring the Temperature of the Product during the Primary Drying Stage of Freeze-Drying," *Drying Technology,* Vol. 16, 1998, pp. 1153-1171.
20. Chouvenc, P., Vessot, S., Andrieu, J., Vacus, P., "Optimization of the Freeze-Drying Cycle: A New Model for Pressure Rise Analysis," *Drying Technology,* Vol. 22, 2004, pp. 1577-1601.
21. Chouvenc, P., Vessot, S., Andrieu, J., Vacus, P., "Optimization of the Freeze-Drying Cycle: Adaptation of the Pressure Rise Analysis to Non-Instantaneous Isolation Valves," *PDA Journal of Pharmaceutical Science and Technology,* Vol. 5, 2005, pp. 298-309.
22. Hottot, A., Vessot, S., Andrieu, J., "Determination of Mass and Heat Transfer Parameters during Freeze-Drying Cycles of Pharmaceutical Products," *PDA Journal of Pharmaceutical Science and Technology,* Vol. 59, 2005, pp. 138-1-53.
23. Velardi, S.A., Rasetto, V., Barresi, A.A., "Dynamic Parameters Estimation Method: Advanced Manometric Temperature Measurement Approach for Freeze-Drying Monitoring of Pharmaceutical Solutions," *Industrial and Engineering Chemistry Research,* Vol. 47, pp. 8445-8457.
24. Armstrong, J.G., "Use of the Capacitance Manometer Gauge in Vacuum Freeze-Drying," *Journal of the Parenteral Drug Association,* Vol. 34, 1980, pp. 473-483.
25. Rasetto, V., Marchisio, D.L., Fissore, D., Barresi, A.A., "Model-Based Monitoring of a Non-Uniform Batch in a Freeze-Drying Process," Proceedings of 18th European Symposium on Computer Aided Process Engineering – ESCAPE18 (edited by B. Braunschweig, X. Joulia), 1-4 June, 2008, Lyon, France. Computer-Aided Chemical Engineering, 25, Paper FP_00210, CD Edition. Amsterdam: Elsevier.
26. Liapis, A.I., Litchfield, R.J., "Optimal Control of a Freeze Dryer – I. Theoretical Development and Quasi Steady-State Analysis," *Chemical Engineering Science,* Vol. 34, 1979, pp. 975-981.
27. Lombraña, J.I., Diaz, J.M., "Heat Programming to Improve Efficiency in a Batch Freeze-Dryer," *Chemical Engineering Journal,* Vol. 35, 1987, pp. B23-B30.
28. Lombraña, J.I., Diaz, J.M., "Coupled Vacuum and Heating Power Control for Freeze-Drying Time Reduction of Solutions in Phials," *Vacuum,* Vol. 37, 1987, pp. 473-476.
29. Sadikoglu, H., Ozdemir, M., Seker, M., "Optimal Control of the Primary Drying Stage of Freeze Drying of Solutions in Vials using Variational Calculus," *Drying Technology,* Vol. 21, 2003, pp. 1307-1331.
30. Fissore, D., Velardi, S.A., Barresi, A.A., "In-line Control of a Freeze-Drying Process in Vial," *Drying Technology,* Vol. 26, 2008, pp. 685-694.
31. Velardi, S.A., Barresi, A.A., "Development of Simplified Models for the Freeze-Drying Process and Investigation of the Optimal Operating Conditions," *Chemical Engineering Research and Design,* Vol. 86, 2008, pp. 9-22.
32. Tang, X.C., Nail, S.L., Pikal, M.J., "Freeze-Drying Process Design by Manometric Temperature Measurement: Design of a Smart Freeze-Dryer," *Pharmaceutical Research,* Vol. 22, 2005, pp. 685-700.
33. Pikal, M.J., Tang, X., Nail, S.L., "Automated Process Control using Manometric Temperature Measurement," United States Patent n. 6,971,187 B1.
34. Gieseler, H., Kramer, T., Pikal, M.J., "Use of Manometric Temperature Measurement (MTM) and SMART™ Freeze

Concludes on page 70.

Dryer Technology for Development of an Optimized Freeze-Drying Cycle," Journal of Pharmaceutical Sciences, Vol. 96, 2007, pp. 3402–3418.
35. Velardi, S.A., Barresi A.A., "Method and System for Controlling a Freeze Drying Process," European Patent application PCT /EP2007/059921 (19/09/2007), 2007.
36. Barresi, A.A., Velardi, S.A., Pisano, R., Rasetto, V., Vallan, A., Galan, M., "In-line Control of the Lyophilization Process. A Gentle PAT Approach using Software Sensors," *International Journal of Refrigeration,* Vol. 32, pp. 1003-1014.
37. Pisano, R., Fissore, D., Velardi, S., Barresi, A.A., "Control of Freeze-Drying Processes of Pharmaceuticals in Industrial Apparatus," *Journal of Pharmaceutical Sciences,* Submitted.
38. Fissore, D., Pisano, R., Barresi, A.A., "On the Design of on In-line Control System for a Vial Freeze-Drying Process: The Role of Chamber Pressure," *Chemical Product and Process Modeling,* Vol. 4, article 9.
39. Barresi A.A., Pisano R., Rasetto V., Fissore D., Galan, M., "Model-Based Monitoring and Controlling of Industrial Freeze-Drying Processes," Proceedings of 16th International Drying Symposium – IDS2008, Ramoji Film City (Hyderabad), India, 9-12 November, 2008, Vol. B, pp. 746-754.

About the Authors

Dr. Davide Fissore is a certified chemical engineer; he received his PhD in 2004 from the Politecnico di Torino. He has been visiting researcher at CPE-Lyon (France) and at the University of Oviedo (Spain). Currently, he is an Assistant Professor at the Department of Materials Science and Chemical Engineering of the Politecnico di Torino (Italy), teaching "Advanced Process Control." His research activity is focused on modeling, monitoring, and control of chemical processes (catalytic reactors working in unsteady-state conditions and processes of separation) and of the freeze-drying of pharmaceuticals. He authored more than 80 papers published on international journals and on proceedings of International Conferences. He can be contacted by telephone: +39-011-0904693 or by email: davide.fissore@polito.it.

Dr. Roberto Pisano is a certified chemical engineer. He received his PhD in 2009 from the Politecnico di Torino (Italy). His research activity is focused on modeling, monitoring, and control of the process of freeze-drying of pharmaceuticals. He can be contacted by telephone: +39-011-0904694 or by email: roberto.pisano@polito.it

Dr. Salvatore Velardi is a certified chemical engineer; he received his PhD in 2005 from the Politecnico di Torino. He has been visiting researcher at CPE-Lyon (France) and assistant researcher at the Politecnico di Torino (Italy). As a scientist, he has worked for DiaSorin (Italy) at the development of lab analyzers for immunological assays. For Rivoira (Praxair Italy) he is involved in the development and design of medical gas systems. He collaborates with the LyoLab research team of the Department of Materials Science and Chemical Engineering of the Politecnico di Torino; his activities include the development of new sensors for freeze-dryers, modeling, monitoring, and control of freeze-drying. He can be contacted by email: salvatore.velardi@polito.it

Professor Antonello Barresi is a certified chemical engineer; he received his PhD in 1990 from the Politecnico di Torino. He has been visiting researcher at Yale (Connecticut, US), professor at the Addis Ababa University (Ethiopia) sent by the Foreign Office as part of International Cooperation program, and "einsegnant invité" at the University of Lyon 1 (France) in 2000 and 2003. Currently, he is full professor at Politecnico di Torino, teaching "Process Design and Development," "Process Control," and "Advanced Chemical Reactors." His research activity concerns drying, mixing in homogeneous and multiphase systems, and combustion (both catalytic and homogeneous). His main research interests in drying include: drying and freeze drying of pharmaceuticals and enzymes, lyophilization of food and damaged paper documents; development of new sensors and control systems for freeze dryers, and modeling and optimization of freeze-drying. He is the author of approximately 90 papers in international journals and more than 100 conference presentations. He can be contacted by telephone: +39-011-0904658 or by email: antonello.barresi@polito.it.

Politecnico di Torino, Dipartimento di Scienza dei Materiali e Ingegneria Chimica, corso Duca degli Abruzzi 24, Torino 10129, Italy.

Miquel Galan is Director of Innovation and R&D of Telstar Lyo in Spain. He has been with Telstar for more than 24 years. He is an expert in pharmaceutical engineering, as well as vacuum technology and leak detection. He has held a position as a process engineering manager, and has managed many large freeze-drying projects. He holds degrees in chemical engineering from the Instituto Quimico de Sarria (IQS) and Industrial Engineering from the Universitat Ramon Llull. He is an active member of ISPE, PDA, and of International Society of Lyophilization - Freeze Drying (ISL-FD). He also is a member of American Society of Mechanical Engineers (ASME), The Pharmaceutical and Healthcare Sciences Society (PHSS), and American Association of Pharmaceutical Scientists (AAPS). He has chaired several freeze drying conferences and lectured on many freeze drying courses, conferences, and workshops, as well as in other topics about vacuum related subjects over the past 15 years. He can be contacted by email: mgalan@telstar.eu.

Telstar-Lyo, J. Tapiolas 120, 08226 Terrassa, Spain.

Customize Your ISPE Email!

Now you can specify your email settings and get the type of email you want from ISPE. Update your Member profile and tell us:

- Your Areas of Interest
- From which groups within ISPE you would like to receive email
- Alternative contact information in case you relocate or change jobs

Remember, your ISPE membership is "portable" and goes with you wherever you work in the industry.

To customize your settings, go online and update your ISPE Member Profile at www.ISPE.org/emailpreferences

Thank you for making ISPE your Society of Choice!

ENGINEERING PHARMACEUTICAL INNOVATION

www.ISPE.org/emailpreferences

Early Bird Ends 12 October

Don't Miss

The Event Of The Year!

Prestigious Keynote Presenters:

- **Samuel Bogoch MD, PhD**
  Replikins, Ltd.
- **Lembit Rägo MD**
  Coordinator, Quality Assurance and Safety: Medicines Essential Medicines and Pharmaceutical Policies at the World Health Organization (WHO)
- **Antonio J. Ricco, PhD**
  Chief Technologist for Small Payloads and Instrumentation in NASA Ames Research Center's Small Spacecraft Division

Eleven Session Tracks:

- Product development
- Facilities and equipment
- Information systems
- Supply chain management
- Production systems
- Regulatory compliance
- Quality systems
- Project management
- Investigational products
- Suppliers
- Survival-focused

ISPE09 Annual Meeting

Thriving In A Survival Environment

8 • 11 November

Manchester Grand Hyatt San Diego
San Diego, California, USA

www.ISPE.org/annualmeeting

Exhibit and Sponsorship Opportunities Available

This article presents new developments in global sourcing logistics and demonstrates how pharmaceutical producers can build an integrated supply and product development strategy.

Building a Flexible, Cost-Efficient Global Supply Chain

by Simon Kaye

Global sourcing in the $500 billion world wide pharmaceutical industry is driven by far more than a temporary search for low cost. It's in fact a long-term systemic trend that necessitates rebuilding of supply chain logistics from the ground up. Building an international logistics system for manufacturers' sourcing needs today requires a quantum leap from past shipping practices, which had grown during decades of relatively stable sourcing and supply trends. The elements that make up the logistics paradigm are constantly changing, and pharmaceutical producers must have a constant awareness of those changes integrated into their total product planning process.

There is too often a notable lack of communication within major manufacturers in all industries, including pharmaceuticals, on concerns that relate to transportation. When a new product idea is conceptualized, researched, and tested, the process involved is detailed and standardized. And when the point of commercializing a new product is reached, producers consider and evaluate the packaging, the marketing, distribution and sales, public relations and advertising. However, transportation and the logistics of the supply chain are taken into account late in the game – if they are ever considered at all. Yet failing to investigate and consider the latest developments in vital logistics factors – shipping trends, customs regulations, and security requirements – can dramatically increase supply difficulties and overall costs for any product, no matter how great its potential demand.

This article will provide a proactive review of behind-the-scenes factors in pharmaceutical logistics as they relate to global sourcing. By examining regulatory requirements and practical business considerations – such as selecting the right freight forwarding partner and specifying the proper shipping terms – we will illustrate the importance of considering the latest developments right from the start to build an effective, integrated supply and product development strategy.

Regulatory Concerns

Pharmaceutical production was born in the pharmacy, but as drug production became a factory process its transport logistics became far more complex. Guidelines established by the US Food and Drug Administration (FDA), the European Medicines Agency, and other regulators for current Good Manufacturing Practice (cGMP) in the production of pharmaceuticals include requirements as they affect raw materials, in-process goods, packaging, labeling and finished goods as well as the manufacturing, testing, documentation, and product release processes. The production of pharmaceutical products requires validating for the FDA every aspect of the receiving, analysis, storage, and handling of drug actives, excipients, and other raw materials. And ensuring cGMP compliance to those standards must be integrated with the normal considerations between supplier and manufacturer. These include demand forecasting, stock levels, production plans, maximum and minimum inventory levels, reorder points, and order quantities.

The supply chain needs for pharmaceutical manufacturing are both complex and delicate, going beyond mere efficiency to require total quality in handling and care. Pharmaceutical companies simply cannot rely on supply sources that use antiquated methods of shipment. For example, it is unacceptable for chemicals or excipients to expire before the manufacturing process takes place, because their shipment was delayed or they were not shipped with proper temperature and humidity control. Additionally, every state has its own license requirements and

Continued on page 74.

Filling instinct.

The time has come to take control. IMA Life introduces the latest technological breakthrough in sterile filling: XTREMA F2000. High performances, superb flexibility and easy implementation allow you to bring your sterile processing environment in line with your production objectives, adapting to your needs as they evolve.
Industry experience, proven technology, IMA Life expertise: ingredients which make the XTREMA F2000 much more than a machine.

www. ima.it/xtrema

PACK EXPO

Las Vegas, NV, USA - October 5-7, 2009
Visit us at Booth # C1819

IMA LIFE S.r.l. • *mktg.filling@ima.it* • *www.ima.it*
IMA NORTH AMERICA, INC. • *sales@imausa.net* • *www.imanorthamerica.com*

IMA LIFE
Aseptic Processing & Filling Solutions

VIAL LOADING • WASHING • DEPYROGENATING • FILLING • FREEZE-DRYING • STOPPERING • CAPPING

timetables for what can come in or out of the pharmaceutical production plant, and when this must happen. License requirements and special storage needs present one of the greatest challenges for both suppliers and third-party logistics partners assigned to build and implement supply chains strong enough to withstand the hardest knocks and unexpected events.

It is estimated that 80 percent of the active ingredients for drugs sold in the US originate in the global sourcing chain outside the country – a fact that received considerable publicity following a number of deaths linked to contaminated batches of the blood thinner heparin originally sourced in China. As a result, there has been growing pressure to disclose much more sourcing information than the existing FDA rules requiring drug companies to disclose the name and location of the manufacturer, packer, or distributor of prescription medications. New labeling standards could include sourcing disclosure for biological agents and bulking agents, each of which has its own supply chain around the globe. The only way this information can be identified and tracked is as the product of an efficient, properly constructed global supply chain.

Intermodal Shipping Concerns

Given the global sourcing of most drug manufacturers, an inefficient supply chain can create unnecessary storage and demurrage charges at ship terminals and airports, caused by information snags, missing or ill prepared shipping documents, and inappropriate cargo routing. The resulting cost penalties can dramatically add to the price of pharmaceutical products by creating huge and unexpected hidden costs. Poor quality of materials and inadequate packaging can lead to wholesale product destruction and poor or incomplete documents can result in delayed shipments. Such messiness when it comes to vendor responsibilities can lead to goods being rejected out of hand during border crossings, customs delays, cargo loss, and outright theft – all of which cost money. Switching cargo to airfreight or expedited airfreight services as a last ditch effort to solve the problem of incompetence and poor preparation may avert total disaster, but at a steep price.

Not understanding the marketplace also can have dramatic repercussions at every stage of building the supply chain. Those pharmaceutical manufacturers purchasing from overseas suppliers must coordinate closely with those responsible for shipping the goods to ensure they are intimately familiar with the customs rules and regulations of every country through which freight will pass, in addition to understanding the associated service parameters and costs. A lack of understanding about the freight marketplace can prohibit the import of vendor shipments or – more likely – add unanticipated customs costs, and possible exam fees. Additionally, a company can incur unanticipated freight costs or surcharges as a result of improper or inefficient routing of cargo.

The Freight Forwarding Relationship

In such a fluid transportation environment, pharmaceutical producers face a critical choice whether to use a local logistics provider or an international one. A local company will be cheaper and may have at least regional network coverage. But it can fall short in IT systems, standardized operations, and relationships with key international shippers. That makes a freight forwarding intermediary a virtual necessity. The best freight forwarders are at the vanguard of new technological advances and cutting-edge supply chain methodology. Their services can be customized for use by both the smallest and largest businesses and corporations. Freight forwarders can often find creative solutions where traditional supply chain handlers see obstacles. When it comes to challenges such as refrigeration, throughput, theft, customs, and other regulations, and product tracking, freight forwarders consistently solve problems in a non-traditional way that adds value.

For example, take the information technology that out of necessity plays a central role in today's evolving pharmaceutical logistics infrastructure, reflecting the emphasis on trace-back systems. An effective freight forwarder will have a computerized tracking system that offers a common language for businesses along the supply chain to capture essential product information and history. It is essential that computerized trace back systems provide an integrated information exchange platform that can be used across the supply chain, enabling information to be retrieved at any stage once a product has been shipped to the drug processor. The ideal program will show what has been shipped, what is in transit, what is due to be shipped, where goods are in the cycle, and how shipment is performing against the manufacturer's timetable. Via links to the freight shipper's own information, customers should be able to cross-check and validate progress and timings of shipments. Such a system will be flexible, and take into account the highly varied documentation and quality standard requirements of multiple national drug safety agencies, enabling one central system to be adapted to many export markets.

A professional logistics company represents the interests of full range of cargo and supply chain nodes. In addition to having a vested interest in the ups and downs of an entire region, freight forwarders have another ace in the hole: the government agencies responsible for customs clearance and other regulatory issues are much more sympathetic to the goals and aims of such a broadly-backed organization. Foreign supply chain networks should not be constructed without relying on seasoned guides who know how to improve throughput, navigate problems, and deal with the governments and ports.

In foreign countries where sourcing cannot be assured of the due process of law, such as China, it is vital to collect data and keep track of all freight in a way that creates a provable and thorough paper trail. Crime, loss, bureaucracy, and corruption must all be taken into account. Electronic tracking from a reliable freight forwarder is often the only way to overcome such roadblocks. Developing personal relationships are essential to understanding foreign business culture, and to cementing agreements between partners who may or may not speak the same language. By taking advantage of established freight-forwarding agents in the region, a pharmaceutical

producer can increase its ability to get results and track its goods effectively.

Hidden Shipping Costs

Working with a trusted freight forwarder also can be instrumental in helping pharmaceutical producers avoid the hidden shipping costs often implicit in the standard **In**ternational **Co**mmercial **Terms** (Incoterms). Incoterms were developed by the International Chamber of Commerce in the 1930s, and have been regularly revised to reflect transportation and documentation changes. They specify the exporting sellers and importing buyer's obligations regarding carriage, risks, and costs, and establish basic terms of transport and delivery. Incoterms only define contractual rights for delivery, and both parties must specify delivery terms and issues such as loss insurance and title transfer. In contrast to newer and smaller importers that generally specify Group C Incoterms (seller arranges and pays for shipping without assuming its risk), sophisticated importers prefer to use Group F terms, such as Free On Board (FOB). Increased supply chain visibility and the control of import shipments are critical FOB benefits. By taking control as cargo crosses the ship's rail at the port of origin, importers get better shipment management from their third party logistics provider.

Importers who are unfamiliar with the implications of Group C Incoterms, such as Cost, Insurance, and Freight (CIF), which designate that the seller pays all charges, may think they are more convenient, because everything is included in the final price. However, this also makes verification of the charges for freight and insurance difficult, meaning that importers generally wind up paying a higher price when the seller chooses the freight company. There are several reasons for this:

- The shipper does not have the vested interest or the leverage to get the best freight price.
- The shipper pays for the insurance, which could include substantial surcharges.
- Currency rates fluctuate widely, and the shipper may charge additional cost to cover them.
- Import quotas, bad weather, and other problems may add additional unexpected cost, which the shipper will cover using a higher rate.
- The shipper will charge a higher rate to cover its administrative costs.
- These and other related factors mean that shippers may build substantial additional freight charges into its rates, which often are not itemized for the importer.

These points all strongly suggest that sophisticated importers prefer to use Group F terms, such as Free On Board (FOB), giving them greater control over their shipments. Increased supply chain visibility and the control of import shipments are critical FOB benefits. By taking control as cargo crosses the ship's rail at the port of origin, importing manufacturers are better able to obtain accurate and timely shipment information through working with the third party logistics provider of their choosing. Because risk and cost transfer from the seller to the buyer in any case, as with CIF, pharmaceutical importers this way are able to manage and control their freight destiny.

The Impact of the CBP

Customs duties represent another source of hidden freight costs that negatively impact unwary companies in their global sourcing. The hidden shipping costs that we've just discussed are one area of concern. Another is the increased costs that will be imposed by new security regulations that will be enforced by the US Customs and Border Protection (CBP) Agency.

The SAFE Ports Act of 2006 directed CBP to gather data about shipments imported to the US that will allow the Agency to better evaluate terrorism and security risks. CBP is now in the process of finalizing rules for an Importer Security Filing (ISF) that requires importers to submit additional security-related information on their shipments at least 24 hours before the goods are loaded on board an ocean vessel. This ISF is in addition to the current 24-hour rule requirement to provide CBP with shipping manifest data in advance of cargo arrival.

It is clear that the ISF will fundamentally alter both the timeline and manner in which import related information is provided to CBP. As plans currently stand, the required filing must be made electronically and include 10 categories

Concludes on page 76.

of detailed identification regarding the manufacturer, shipper, consolidator, and importer, as well as information on the shipping container stuffing location and various shipment identification numbers. This information must be provided as individual line items so that shipments which contain merchandise subject to multiple classifications will require multiple ISF submissions. In addition, the carrier must provide CBP with two other items: a cargo stowage plan for the vessel, and container status messages. Thus, the ISF requirement is being referred to as the "10+2" rule.

The Import Security Filing will dramatically alter the supply chain information requirements. It is anticipated that the party who makes the ISF is responsible for the timeliness and correctness of the transmission, and must make every effort to verify the correctness of the data and to update the filing if there is any change in the data while the merchandise is in transit to the United States. Although some of the required data elements can be obtained from existing purchase order systems, most companies will be required to coordinate information from several different sources to satisfy the ISF requirements. It is not certain when the ISF requirements will be final, but it is clear that they will require importers to make major changes in how they gather and report information about their shipments. Such considerations will make partnership with a technologically sophisticated freight forwarding specialist even more necessary.

Security Impact on Air Cargo

The Importer Security Filing involves ocean shipping, but this is not the only link in the supply chain where security concerns will soon add greater complexity. In August 2007, President Bush approved the Implementing Recommendations of the 9/11 Commission Act of 2007. This legislation mandates 100 percent security screening of all cargo transported on passenger aircraft – a method of shipping that is often crucial for pharmaceutical producers and many other companies needing rapid or last minute shipments. It's estimated that this involves some 15 million pounds of freight daily, all of which must now be subject to a level of security screening commensurate to that of passenger baggage. The Transportation Security Administration (TSA) is responsible for the screening, which also will apply to cargo-only aircraft.

By August 2010, 100 percent of air cargo must be screened by TSA-approved methods prior to being loaded on a passenger aircraft with a preliminary requirement of 50 percent screening by February 2009. Screening must be done by breaking down pallet-wrapped shipments (PAX) into individual items with the number of pieces determined by shipper-level documentation. Screening can be by physical examination, x-ray examination, or using electronic explosives detection methods. Screening capacity at a single point in the supply chain is not sufficient to accomplish this requirement – and significant carrier delays, cargo backlogs, and transit time increases are expected.

TSA is pursuing a Certified Cargo Screening Program (CCSP) to allow screening of cargo early in the air cargo supply chain by a trusted, vetted, and audited facility. A facility approved for CCSP status must establish the integrity of a shipment through enhanced physical and personnel security standards, and verify the integrity of a shipment throughout the supply chain by utilizing stringent chain of custody methods. CCSPs can be located at shipping facilities, third-party logistics providers, warehouses and distribution centers, freight forwarding facilities, or manufacturing facilities. Certification is currently under way, and even pharmaceutical processors that do not frequently use air cargo would be well advised to establish a CCSP relationship.

It is certain that the new regulations will have an impact on cold chain logistics management for vaccines and other biologics shipped by air. Cold chains must operate by a quality management system in which maintenance of required temperatures is documented and verified through appropriate thermal testing. In today's methodology, certified test labs use environmental chambers to simulate ambient profiles that a package may encounter in the distribution cycle. Thermocouple probes measure temperatures within the product load to assure that temperatures do not reach outside of the required temperature range. However, the screening required under the new regulations could disrupt the necessary temperature assurance unless performed and documented under controlled conditions – another argument for partnering with a top quality CCSP freight forwarder.

Flexibility and Foresight

This discussion certainly doesn't encompass all the key considerations that pharmaceutical companies should consider in building their supply chains, but it does indicate that flexibility and foresight are essential to keep logistics problems from occurring in today's rapidly changing logistics landscape. Problems are inevitable for the unprepared or unsophisticated company that hasn't made supply chain design a priority. A well constructed supply chain doesn't just happen. It requires planning and analysis that encompasses all customer interactions from order entry through paid invoice, all product transactions, all regulatory requirements, and all market interactions for the final fulfillment of each order.

About the Author

Simon Kaye is Founder and CEO of Jaguar Freight Services with offices in London, New York, Philadelphia, Paris, Brussels, and Hong Kong, and an operations network in Europe, North America, South America, Australasia, Asia, Middle East, and Africa. Jaguar Freight Services provides a fully integrated door-to-door freight solution, including customs clearance, storage, and distribution facilities, and proprietary **Cybertrax**, real time online information tracking system. He can be contacted by telephone: +1-516-239-1900 or by email: simon@jaguarfreight.com.

Jaguar Freight Services, Ltd., 10 Fifth St., Suite 303, Valley Stream, New York 11581, USA.

In safe hands

Containment Solutions for the Pharmaceutical & Biotech Industries

- Barrier Isolation Systems
- Downflow Containment Booths
- High Containment Screens
- Pack Off and Process Equipment
- Kilo Labs & Glassware Enclosures

howorth
air technology

For further information please contact us on
North America 502 968 2065
Rest of the World +44 (0) 1204 571131
info@howorthgroup.com www.howorthgroup.com

ISPE's President reflects on the past 25 years of the Society's incredible history and discusses the challenge to become truly global; the importance of becoming a trusted technical resource for Members and regulators; and positioning the Society for success in the future.

PHARMACEUTICAL ENGINEERING Interviews

President and CEO, International Society for Pharmaceutical Engineering, Bob Best

Q Tell us about your educational background.

A I have two degrees in communications/marketing from the University of Notre Dame. I earned my undergraduate degree in 1972 and was able to complete my master's in 1975, while I was working for the University.

Q How did you begin your career?

A I started as a journalist with the Cincinnati Post and Times Star. I moved from there into public relations with Major League Baseball's Pittsburgh Pirates. I then went back to Notre Dame in a sports communications position before becoming the Director of Public Relations and Marketing for the Tampa Bay Buccaneers of the National Football League.

Q What prompted you to make a career change from what appears to be a very exciting job?

A I decided to make a change after 14 years in the sports world. There is no doubt that the sports industry is exciting. I enjoyed my years in it and consider myself fortunate for having had that opportunity. However, if you are not an athlete or a relative of team ownership, the chances for advancement are limited. At the age of 34, I felt it was time for me to move into the "real world" and find something with growth potential. I am not sure the "association world" fully qualifies, but it is a lot more real than the sports/entertainment industry and the Members we serve are performing a very real, critical function. In addition, my family and I also enjoyed living in the Tampa area so I looked for a position that would utilize my skills and experience and keep us in the area. ISPE was looking for an Executive Director and at that time, it appeared they were mostly in need of a marketing and operations person. I felt like it could be a good fit. ISPE was beginning its fifth year with lots of potential, but also lots of debt and doubt about its prospects for survival. I was looking for a new challenge and ISPE offered a significant one. I thought it would be something I would do for two or three years and then move on. Twenty-five years later, here I am!

Q How did you find out about ISPE?

A A friend of mine who knew I was looking for a career change had seen the job advertised and told me about it. I applied in October, was interviewed in early November during the ISPE Annual Meeting, which happened to be held in the Tampa area that year, was hired a week later, and began 2 January 1985.

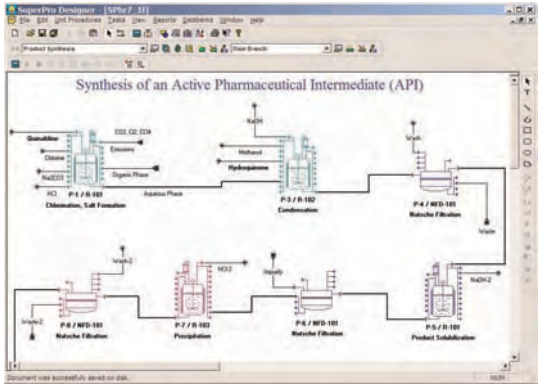
Q What has been the single most exciting success in your 25 years?

Continued on page 80.

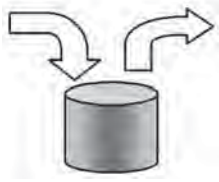
Intelligen Suite

The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Single & Multi-Product Facilities

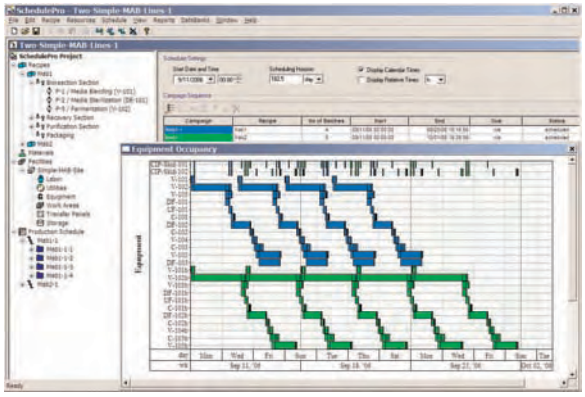
SuperPro



Use SuperPro Designer to model, evaluate, and debottleneck batch and continuous processes

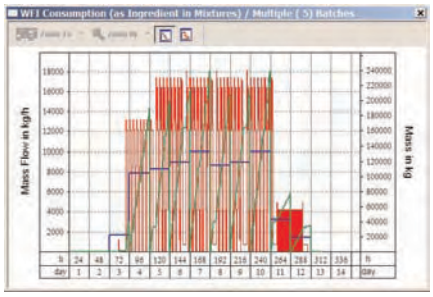


SchedulePro

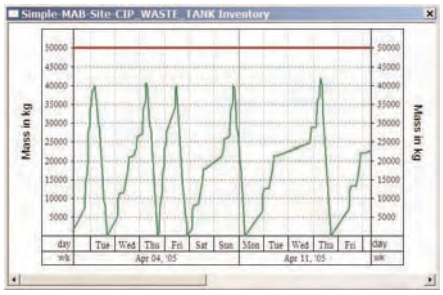


Switch to SchedulePro to schedule, model, and debottleneck multi-product facilities

Tracking of equipment occupancy in multi-product facilities



Tracking demand for resources (e.g., labor, materials, utilities, etc.)



Inventory tracking for raw materials, intermediates, products, and wastes

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of biochemical, specialty chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 400 companies and 500 universities around the world (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile finite capacity scheduling tool that generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of facilities, equipment, resources and work areas. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size utilities for batch plants, identify equipment requirements, reduce cycle times, and debottleneck facilities.

Visit our website to download detailed product literature and functional evaluation versions of our tools

INTELLIGEN, INC. • 2326 Morse Avenue • Scotch Plains, NJ 07076 • USA
Tel: (908) 654-0088 • Fax: (908) 654-3866
Email: info@intelligen.com • Website: www.intelligen.com
Intelligen also has offices in Europe and representatives in countries around the world

"I think the biggest change is happening right now. Our industry is going through a major transition, both in its business model and technologically. Our strategic plan written three years ago forecast this and thrust us into a role as innovator, a catalyst for change."

A Wow! That is a tough one. In this business, everything is a team victory and I don't think we have sufficiently celebrated several impressive successes in ISPE's 29 years of existence. The Society started as essentially a USA educational organization. But in a relatively short amount of time, we have become truly global, no small feat for a not-for-profit organization. And both the industry and its regulators have come to rely on ISPE for the technical solutions we have been able to develop, thanks to some incredible dedication by hundreds of ISPE Members. So I believe our greatest accomplishments are becoming global faster than anyone could have projected and to have evolved beyond education into a role of creating valued standards for the industry.

Let me add that I do not believe that people fully comprehend how remarkable our growth has been, geographically and in program scope. Individual membership not-for-profit organizations like ours are constantly revenue challenged. The fact that we have Affiliates in 32 countries and Chapters throughout the USA, that we offer the range of services beyond the original intent and are only 29 years old is absolutely amazing. Sometimes we need to step back and reflect upon that.

Q How are we following up/expanding on these successes?

A Well, we have Affiliates and Chapters in nearly every key pharmaceutical region in the world. Yes, there are some countries left, but I believe we are very well positioned in that regard. I think we are capable of taking on even more responsibilities for the industry and the regulators, perhaps serving more extensively as a technical option to the major industry trade associations and to ICH.

Q What has been the most impactful change in the industry over the past 25 years? How did ISPE respond?

A I think the biggest change is happening right now. Our industry is going through a major transition, both in its business model and technologically. Our strategic plan written three years ago forecast this and thrust us into a role as innovator, a catalyst for change. Our Product Quality Lifecycle Implementation (PQLI) initiative is an example of how we can fulfill that role.

ISPE has gained respect, worldwide, and we are seen as a neutral body. That enables us to be an effective integrator. We have been successful in that regard by integrating industry and regulators on a scientific/technological level. We have done the same between operating companies and suppliers of service and equipment, taking the position that visionaries from all of those entities are part of the ultimate solution. We might also be able to serve as an integrator among traditional pharmaceutical, generic, and contract manufacturing companies, where I believe there is a need for someone to play such a role.

Q Looking back, is there a specific decision/direction that you would have done differently?

A I do not know any organization, armed with 20/20 hindsight, that cannot identify a whole host of things they would have done differently. In our case, I would say that most such cases would be related to saying "yes" to nearly every new initiative that comes our way. Ironically, that has also been a key to our success, but at the same time, it has also created resource issues which have been troublesome at times.

Q What has been the most significant impact that ISPE has had on the industry?

A I would have to say our technical documents. The Baseline® Guides and GAMP® 5 have become industry standards. The Baseline® Guides are the result of ISPE's integrator capabilities. Back in the 1990s, industry leaders believed that there were some dramatic misconceptions about FDA expectations on GMPs. They asked ISPE to arrange a dialogue with the FDA to either verify or refute these matters. The end result was an agreement for ISPE to provide the technical input, for FDA to review and comment, and for ISPE to deliver a document that reflected these conclusions that both industry and FDA could rely on for clarification. The Baseline® Guides have become a tremendously valuable tool for our industry. The GAMP® series has been similarly impactful.

Q Why did the FDA choose ISPE as the hub of the wheel that makes our industry turn?

A I am not sure we are the "hub of the wheel," but that is a nice sentiment. I do believe we have become a trusted technical resource in the eyes of the leaders of the FDA and that a similar perspective is spreading among regulatory authorities in Europe and Asia Pacific.

We are a non-lobbying group designed to serve all constituencies with neutrality, which means both industry and the regulators can rely on us because we have no agenda other than providing solutions. We are an individual membership organization not controlled by companies, but guided by the input of a diverse membership. We are truly global and few other organizations can claim that. We deliver. Our Members have taken on some important projects and in a relatively short period of time come through with tangible results.

I think the real break through for us was with the SUPAC Equipment Guide that we produced at the request of the FDA. They recognized that they had a need that they could not practically fulfill internally. They turned to us and we came through on a pace and at a level of performance that were truly remarkable.

Q What has been the secret to the success of ISPE over the past 25 years?

A **Collegiality.** ISPE is an organization that makes good things happen. Our Members and our staff are focused on helping others. I am amazed at the team attitude that pervades ISPE, especially having come from the sports world where egos are rampant. The attitude in this organization has been "If there is a need, let's find a way to deliver and not be concerned about who did what . . . just make it happen, just fix it." That is part of our culture, as is making sure that people feel welcome the very first time they show up at an ISPE activity. Our Members have always been willing to share, to help another Member find a solution to a problem. I have witnessed that in places where I was told that sharing was not a cultural norm. Well it is in the DNA of ISPE.

Commitment. When I started at ISPE the Society was $400,000 in debt. All the Members of the Board of Directors at that time had just signed for a loan, personally guaranteeing it. Can you imagine a stronger degree of commitment? Fortunately that sort of thing has not been required in recent years, but the dedication of our leaders, from directors on the International Board, to leaders of our many Affiliates and Chapters and the hundreds of committee, COP, and writing task teams, Members remains a strength of this organization. And let me add that such dedication has always been matched by our staff and advisors. The people who have worked for ISPE over the years could have been more highly compensated at other places of business. But they have chosen to be at ISPE because they recognize it as a special place. The chemistry between the volunteers and staff has been infectious.

Q How is ISPE recruiting and engaging regulators at the international level, other than FDA, EMEA, etc.?

A Among our many blessings has been to have some incredibly talented, well liked, and well connected former regulators involved as Members of our Regulatory Affairs Committee (RAC) and as our Regulatory Affairs Advisors. This started with Joe Phillips, who passed away suddenly last year, but who had made an incredible impact for ISPE over time. Joe had been employed by the FDA for 44 years and had been active on their behalf internationally. When he joined ISPE as an advisor he solidified and expanded our relationships here in the USA, but also in Europe and Japan.

Continued on page 82.

In Asia Pacific, Bob Tribe is our Regulatory Affairs Advisor. Bob not only held a senior position with Australia's TGA for more than 30 years, but he if a former Chairman of PIC/S. Upon his retirement from TGA, he became a consultant for PIC/S, WHO, and ISPE. And in Europe, John Berridge is our Regulatory Affairs Advisor. John is not a former regulator, but rather a senior manager from industry. However, he had been actively involved in ICH activities as a representative from EFPIA and in that capacity developed an excellent network within Europe and also among the other ICH regulators.

These gentlemen, former regulators Chuck Hoiberg and Paul D'Eramo, and current ICH participants Bob Baum and Georges France, all of whom are members of the RAC, have opened many doors for ISPE. In addition, I spend a great deal of my time expanding relationships on the regulatory front, especially in Asia.

Q Where do you see the Society five to 10 years in the future?

A Had you asked me that question a year ago I could have given you an answer with some confidence, though I would have probably been proven wrong. I do a lot of reading and listening and I must say the future is a bit cloudy. Certainly the current economic recession, which has had such a dramatic impact on all industries, will eventually swing in the opposite direction, as it always does, and that will have a positive affect. However, it is the current transition of our industry that is a little less clear. As I am doing this interview our leadership is preparing to meet to make just such a projection. We have done our homework and I am confident we will settle on a vision of where the industry is headed that will turn out to be accurate.

One thing is certain. Our industry will be much different 10 years from now than it is today. That might sound obvious, but frankly for my first 25 years with ISPE our industry has changed very little. I am pleased to say that the ISPE leadership has been very good at strategic planning, so I am confident our planning sessions will result in a clear direction for ISPE, one that will position the organization for success as the industry evolves.

Q Why is ISPE based in Tampa, FL?

A The two men who originally conceived of ISPE, Don Cattaneo and Paul Simmons, lived in Tampa when ISPE began in 1980. They did most of the initial startup work and incorporated ISPE in the state of Florida. As you would expect, the organization started with no funding and back in the 1980s, Tampa was an inexpensive place to operate.

Right before I was hired, the Board of Directors actually considered the possibility of relocating the Society to New Jersey, the center of the industry in those days. However, when they did the math, they determined that the Society could not afford to make such a move so ISPE remained in Tampa.

Because of the way business is done these days it really does not matter where an organization like ours is located since so much of what we do is accomplished electronically.

Q Who do you view as our main competition and what sets ISPE apart?

A Within the not-for-profit arena, it is hard to think in terms of "competition" in the traditional business sense. ISPE was started because there was a niche . . . technical professionals . . . that the founders believed was not being well served. That remained true for about the first 15 years. Then several enterprising for-profit educational groups and publications recognized an opportunity and started to produce programs similar in content to ours. That trend continues today and they do represent a competitive threat to us.

There are other associations that overlap to an extent, both in programming and membership base. Whenever possible, we try to work with them for the good of the industry. As a volunteer driven organization, we consider our leaders' time precious so we must be sensible, especially at this point in our history, to eliminate redundancy whenever possible. Companies are less able to sponsor their employees to work on the types of projects we are engaged in so we must do our best to ensure we are not overlapping in what we attempt with other organizations.

Q Where will ISPE's international growth be in the future?

A As I mentioned, I believe we are already well positioned thanks to the dedication of hundreds of leaders from our Affiliates around the world. However, based on the anticipated expansion of the industry into Asia, Eastern Europe, and Latin America, clearly our greatest opportunity for growth will come from those regions.

Q What have been the challenges in developing the international Affiliates?

A Frankly, after scaling the mountain of expansion into Europe in the early 1990s, it has been mostly downhill from there. The learning curve and growing pains in establishing the Society in Europe were immense. For ISPE, we were inventing a wheel. We had no experience in starting a business in Europe, few Europeans on hand to guide us at that time, and precious little funding. Expanding any business into a new continent is complex and expensive, even with a road map in place. We made up most things as we went along. Fortunately, in addition to our ignorance, we also had the belief that this was the right thing to do and the commitment to stick it out. More importantly, as has always been the case, we found people in all the Affiliate countries who became passionate about ISPE, so much so that they overlooked our operational short-comings and gave us the wisdom to enable us to succeed.

With all the errors that we made along the way, we did make one decision that was the most important of all. Unlike other American based groups that

expand overseas and attempt to impose US ways of doing things, we wanted the Affiliates to develop programs and approaches that were appropriate to their countries. Certainly, there were some processes that had to be consistent throughout the Society, for Affiliates and Chapters, but those were and continue to be relatively few. I believe our Affiliates and Chapters have been able to operate fairly independently and be innovative in their areas.

Interestingly, we have learned that as different as we believed Europe is from North America, Asia is even more complex from a business perspective. Fortunately, the experiences in Europe taught us to be flexible in our planning. Now that we have a critical mass of Members and Affiliates in Asia Pacific we have determined that it will be essential to regionalize our approach to best serve our Members and assist our volunteer leaders. We are changing our strategic and operational plans to accommodate this thinking.

Q Have you visited all the Affiliates?

A I have been to all but five and have had a hand in launching the majority of them. For me, that has been one of the most rewarding experiences in my life. Meeting people from all over the world, learning about their cultures, business customs, and legal systems, and then working with them to establish something worthwhile will be something I will remember and value for the rest of my life.

Q What do you do on a routine basis – what is a typical day like for you?

A I frequently reflect about the way the answer to that question has changed over the years. When I started in 1985, I was one of four full time employees. For probably the first 15 years here, I spent almost the entire day on the phone. I remember the staff joking about how they would race over to my office when they saw the light on my phone line go off so they could catch me between calls. Now, I spend almost my entire day, and lots of the night, sending and replying to emails.

Certainly, I have specific projects that I initiate, mostly strategic initiatives and business development tasks. But I consider myself an enabler, both for staff and our volunteers. I believe the most important thing I can do is to get information in the hands of those doing the work of the Society. I feel especially strong about that when it comes to the volunteers. If someone is trying to do good work and they need input from me in order to accomplish it, I need to get that to them as quickly as possible. So I am passionate about returning emails quickly. As a global organization, those emails come in 24 hours a day so I try to be responsive early in the morning before I come to the office, throughout the day, and at home at night.

Beyond that I spend a great deal of time with the staff, those in the

Concludes on page 84.

headquarters office and in our offices in Brussels, Singapore, and Shanghai. I have several direct reports, but also try to be available to other departments that might need my assistance.

Not surprisingly because of our global reach, I travel about one third of my time, much of it outside the USA.

Q How is ISPE responding to the current economic climate?

A We expected hard times were coming, but the enormity of the global recession made the impact far worse than anticipated. Fortunately, we had accumulated a cash reserve for just a situation. We started with a lean budget for 2009, but have made 17% in expense cuts from that. As with many other companies, regrettably, this has included a reduction in staff. We have been careful not to make reductions that would adversely impact our ability to deliver the tools and services our Members have come to expect from us.

Since volunteers are the ones responsible for the true gold nuggets ISPE provides . . . knowledge . . . we must also keep a close eye on their constraints. Many companies have imposed travel restrictions so we have had to quickly redesign many of our SOPs to accommodate that reality.

They say that you test the true metal of a person or organization during tough times. If that is true, I am now even more convinced of the viability and longevity of ISPE. Our volunteers and staff have absolutely risen to the occasion. I have witnessed our best thinking and strongest efforts this past year. We will come out on the other end as a more efficient organization and more closely targeted to the needs of our Members.

Q What are the major challenges running an organization of volunteers? How do you motivate the volunteers?

A I cannot take credit for that. ISPE has always had a long line of people passionate about the organization, visionary in the ways to improve it, and committed to the tasks necessary to succeed. We on the staff are here to make that as easy and effective as possible, but few are the times when we have to "nudge" the volunteers to action.

Q How have you been able to maintain such a loyal staff in Tampa?

A I guess you probably need to ask them. I am proud that we have had so many people stay with ISPE for a good part of their career, and make significant contributions along the way. I try to give the staff the ability to apply their own styles to their positions, establishing some goals for them, but then getting out of their way. I am genuinely concerned about every person who works for ISPE, in all of our offices, and will always do whatever I can to help them succeed, preferably with ISPE, but wherever they may decide to go.

Q What is the purpose of the International Leadership Forum (ILF)? How has it positively impacted ISPE?

A The ILF is actually the 21st century version of what was known as the Pharmaceutical Advisory Council (PAC). The PAC started in the early 1990s and was made up of Vice Presidents of Engineering from the multinational companies based in the USA. It was this group that motivated the development of the Baseline® Guides, as I discussed earlier. As ISPE expanded, both beyond its initial focus on "engineering" and also geographically, the leaders of the PAC believed that body needed to be reconfigured. So now the membership constituency includes Presidents or Senior Vice Presidents with global responsibility, in the areas of quality, engineering, manufacturing, and development, from pharmaceutical, biotech, generic, and contract manufacturing companies, from all over the world. They have been incredibly helpful to the Society, in particular to our strategic planning, but also in providing resources, mostly in terms of contributors to our Body of Knowledge. As the years have gone by, they have become even more hands on. They were the motivators of Product Quality Lifecycle Implementation (PQLI) initiative and have recently begun work on an important Supply Chain Security project.

Q What will be your legacy to ISPE?

A If you are looking for specific metrics I suppose it would be development of a truly global organization and a sound business foundation. When I started, we had 500 Members, were badly in debt, and aside from a handful of international Members were completely USA centric. Today, we have 24,000 Members in 90 countries and despite the impact of the global recession have significant reserves. Certainly, I am proud of that, and do believe I have made a contribution toward it. But my primary contribution has been as a facilitator, spotting a whole lot of talented people, getting them into the right slots, and letting them make things happen for the truly vibrant organization that ISPE has become.

Q What interests you/keeps you busy in your personal life?

A So you saved the most sensitive question for last. ISPE has been a very important part of my life for a quarter of a century. I would like to think my family has always ranked first, but the demands of running an international organization as complex as ours often take me away from them. So when I am home I try to do the things they want. They are my interest. Early next year those interests will expand. My daughter is expecting a child in January so my wife and I officially jump into a new generation in our family. I relish the thought of becoming a grandfather.

On a rare occasion, I manage to sneak out on the golf course. I am a current events fanatic and read as much as I can and watch news outlets that I consider reliable and worthwhile. And as you might expect from my previous "life," I remain a sports fan.

Annual Meeting to Focus on Thriving in a Survival Environment

The 2009 ISPE Annual meeting will be held 8-11 November in San Diego, California, USA. This year's theme is Thriving in a Survival Environment. The following are highlights of what to expect at the Keynote Session and in 11 topical tracks:

Keynote Session

This year's Annual Meeting Keynote Speakers are:

- **Samuel Bogoch MD, PhD,** is chairman of Replikins, Ltd., in Boston, Massachusetts, USA, and faculty at both Harvard Medical School and the Boston University School of Medicine. Dr. Bogoch's areas of research include chemical structure and virus receptor properties of brain gangliosides, inhibition of virus attachment to brain cells, structure and function of brain glycoproteins, biochemistry of cancer, serum antibodies to cancer antigens, the replikins, genomic peptides associated with rapid replication, quantitative relation of replikins to virus outbreaks, and advance warning of H5N1.
- **Antonio J. Ricco** is Chief Technologist for Small Payloads and Instrumentation in NASA Ames Research Center's Small Spacecraft Division, on loan from Stanford University's Department of Electrical Engineering and Center for Integrated Systems. At NASA, Ricco develops remote, autonomous bioanalytical systems for fundamental space biological studies; serves as chief technologist for the GeneSat, PharmaSat, and O/OREOS flight projects; and is instrument lead for the MEMS-based NIR spectrometer on the LCROSS lunar impactor. Ricco is Vice President of the Transducer Research Foundation and a member of NASA's Lunar Exploration Analysis Group.
- **Lembit Rägo MD, PhD** is Coordinator, Quality Assurance and Safety: Medicines Essential Medicines and Pharmaceutical Policies at the World Health Organization (WHO) in Geneva, Switzerland. In December 1999, he joined the WHO in the Department of Essential Drugs and Medicines Policy where the areas of medicine nomenclature, quality standards, regulatory guidelines, safety and pharmacovigilance, are addressed. Since 2000, he has been the WHO observer to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Steering Committee.

Education Sessions by Track

Many of this year's education tracks correspond to a Certified Pharmaceutical Industry Professional™ (CPIP™) Knowledge Element. CPIP is a competency-based international credential. Please visit the Annual Meeting section on the ISPE Web site for a listing of sessions in each track.

- **Survival**
  ISPE education sessions are created by ISPE Members who work every day in the same environment that you work and face similar challenges. As Volunteers, ISPE Member presenters bring their ideas to the Annual Meeting table sharing knowledge, insight, and application through these education sessions, aiming to strengthen the pharmaceutical environment through this medium.
- **Product Development**
  (CPIP Knowledge Element 1)
  CPIP Knowledge Element One includes: formulation, clinical phases, and manufacture; technology transfer; production scale-up and optimization.
- **Facilities and Equipment**
  (CPIP Knowledge Element 2)
  CPIP Knowledge Element Two includes: design and construction/installation; commissioning and qualification as a risk management strategy; operation and maintenance; controls and automation.
- **Information Systems**
  (CPIP Knowledge Element 3)
- **Supply Chain Management**
  (CPIP Knowledge Element 4)
  CPIP Knowledge Element Four includes: materials management; operational economics; warehouse and distribution management.
- **Production Systems**
  (CPIP Knowledge Element 5)
  CPIP Knowledge Element Five includes: production unit operations – drug (small molecule) and biologics; production management; production control.
- **Regulatory Compliance**
  (CPIP Knowledge Element 6)
  CPIP Knowledge Element Six includes: government regulations; standards, practices, and guides.
- **Quality Systems**
  (CPIP Knowledge Element 7)
  CPIP Knowledge Element Seven includes: risk management and Quality Management System (QMS); systems validation.
- **Investigational Products**
  The Investigational Products (IP) Community of Practice (COP) brings together industry professionals for interactive learning and networking opportunities. This year's sessions include educational topics that address challenges industry professionals face in their day-to-day lives, as well as emerging or strategic topics important for managers and decision-makers.
- **Project Management**
  The PM Community of Practice (COP) has chosen two distinct, large-scale projects to feature through six highly-interactive sessions for the Project Management Track.

Concludes on page 87.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

ILF Takes on Challenge of Global Supply Chain Integrity

The integrity of the pharmaceutical supply chain is becoming the focus of increasing concern and scrutiny. The supply chain is becoming more complex, the number of environmentally sensitive products is rising sharply, and the sophistication of counterfeiters is alarming. Consequently, the industry is facing increasing legislative scrutiny and guidance on ensuring the quality of its products throughout their entire lifecycle.

ISPE's International Leadership Forum (ILF) has established a Global Supply Chain Integrity workgroup to develop a guide that describes globally applicable practices to help secure the integrity of the pharmaceutical supply chain.

These practices include quality system and security practices that help prevent adulteration of products in the supply chain or the introduction of counterfeit products into the supply chain. The guide will also address practices that help prevent the diversion of products outside of legitimate channels of commerce. These illegitimate channels can result in the adulteration of products or the introduction of counterfeits into commerce. It will also cover the use of information to signal potential supply disruptions that could encourage the use of substandard or substitute materials by suppliers. The guide will also make recommendations on steps a firm should take when a signal of potential supply disruption is detected.

A second workgroup will develop an outline for a paper or document that describes technical standards for anti-counterfeiting measures and more detailed methods only covered in general in the guide.

ISPE's ILF provides an opportunity for thought leaders in the pharmaceutical industry to identify and influence direction and align the industry globally, establish dialogue with regulators to discuss critical technological issues, identify opportunities for innovation, promote consistency, and seek worldwide harmonization where appropriate. PE

Annual Meeting...

Continued from page 86.

- **Supplier-Focused**
  Suppliers offer a superb knowledge resource. This year, sessions of particular interest to suppliers are listed as a track to recognize this important facet of ISPE educational programming. PE

ISPE Launches Operations Management Community of Practice

ISPE has launched the Operations Management Community of Practice (COP). This new COP aims to cover and review all areas of operations management including the integrated process flow, from raw materials supply to final product distribution. The goal is to better understand how a complex pharmaceutical manufacturing plant can work more efficiently to increase productivity.

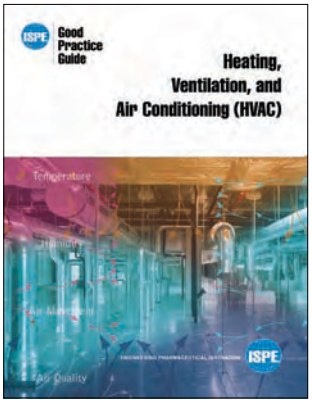
"In the past, pharmaceutical companies have always considered manufacturing as a matter of compliance with regulatory requirements (GMP)," said Operations Management COP Chairs Giuseppe Ravizzini and Alain Cruset. "Currently, due to decreasing rate of innovation, increasing costs for R&D and increasing variety of customer preferences, operations have started to implement tools and methodology to improve performance and efficiency."

"It is essential to learn from other industry sectors, to improve industry sectors, to improve technological and management aspects, from strategic issues to planning and shop floor execution."

The COP has identified 10 main areas of competence that the group will focus on in future discussions, meetings (on the Web or live), work teams and other initiatives. To read more about these areas, you can visit the Operations Management COP by following these instructions:

- Log in at www.ispe.org/cops
- Click on Join/Unjoin COP
- Scroll down to Operations Management COP and place a check mark in the box
- Click the "Join" button in the bottom right corner

HVAC Guide Helps Determine User Requirements and Functional Design



Heating, Ventilation, and Air Conditioning (HVAC) systems are employed for human comfort and to protect people and product. HVAC systems also can protect the outdoor environment from hazardous material removed from the work place via HVAC exhaust.

HVAC systems can be critical systems that affect the ability of a pharmaceutical facility to meet its objective of providing safe and effective product to the patient. Systems that are properly designed, built, commissioned, operated, and maintained can help ensure the quality of product manufactured in that facility, improve reliability, and reduce both first cost and ongoing operating costs of the facility.

In the pharmaceutical industry, HVAC design engineers need to deliver a GMP compliant design for a particular process application that meets key customer requirements and complies with local codes and standards. To successfully deliver such a design, the HVAC engineer also must understand how those systems integrate into and are affected by other aspects of the facility design and operation. The HVAC engineer must coordinate with other disciplines for a successful project.

The ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC), expected to be released in October, provides designers and the project team with suggestions to help determine the user requirements and the functional design that define the facility's objectives. It also provides options to be considered in creating a design that has low lifecycle cost and which is sustainable.

ISPE Singapore Conference 2009 a Success

With the theme of "Advancing Excellence and Innovation in Regional Pharmaceutical Manufacturing," the ISPE Singapore Conference 2009 was held 31 May – 2 June at the Suntec Convention Centre, Singapore. Eight facility visits were also organized for delegates on 3 June.

Attended by 216 registered delegates from the region participated in a program that included topics relating to sustainable solutions, regulatory, automation, manufacturing excellence, contract manufacturing, and validation.

Affiliate representatives of all nine Affiliates (Australasia, China, India, Indonesia, Japan, Korea, Singapore, Philippines, and Thailand) in Asia Pacific gathered in Singapore for the Asia Pacific Affiliate (APAC) meeting on 2 June, held alongside the ISPE Singapore Conference. Leaders discussed the possibility of collaborating on regional training programs and conducting potential webinars that would be of interest to industry professionals in Asia Pacific. The Affiliate leaders also explored various approaches of promoting to the region benefits of ISPE's Communities of Practice (COPs) and Certified Pharmaceutical Industry Professional™ (CPIP™) program.

The meeting concluded with dialogue with Jacques Morenas, Assistant Director of the Inspection and Companies department in the French Health Products Safety Agency (AFSSAPS) and chair of the Pharmaceutical Inspection Co-operation Scheme (PIC/S).

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

Online Learning Conveniently Delivers Quality Education

These days, time is more valuable than ever and sending just one employee to attend an offsite education program is more than most work schedules and company budgets can handle.

Alternative, more convenient ways of educating employees need to be available to companies, and ISPE offers such options through its Online Learning Program. The same quality education found at an offsite event is delivered by computer with Internet access.

Industry and regulatory professionals working in the field develop and lead ISPE Online Learning events and courses, so learning comes straight from experts with current knowledge and cutting-edge perspectives. For a broad range of choices, ISPE divides its forms of Online Learning into these families:

Live Webinars – Real-time presentations by industry experts and regulatory professionals.

Recorded Webinars – Recorded versions of live webinars. Participants can take the time they need and enjoy important presentations at their convenience.

Webcasts – Video recordings of ISPE conference education sessions.

Podcasts – ISPE education and information briefs for hand-held devices.

Online Courses – On-demand learning for fundamental to advanced knowledge on relevant and timely subjects, and to help meet regulatory training requirements. Interactive learning experience includes a downloadable course presentation, learning reviews/assessments highlighting important points, hot-links to information, and an online resource handout as a quick reference.

Basic Industry Knowledge and Certified Pharmaceutical Industry Professional™ (CPIP™) Online Courses – Self-directed courses providing a range of learning opportunities for career growth and professional development. For those interested in general pharmaceutical industry knowledge on topics ranging from drug product development to manufacturing, and those seeking the CPIP™ (www.ISPE-PCC.org) credential.

GMP Online Courses – Education on different standards, laws, regulations and guidelines impacting GMP compliance and quality.

Product Quality Lifecycle Implementation® (PQLI®) Webinars – Sessions with subject matter or discussions tied to the PQLI initiative (www.ISPE/org/PQLI).

Aside from an employee being in the same room as a presenter, ISPE Live Webinars are no different from an offsite conference seminar or training course. Participants listen to discussions as they would in a classroom, and have the opportunity to directly question and answer speakers on the other end of the live event. Plus, novel, interactive features such as polling and voting during discussion are available.

At only $79 for ISPE Members ($179 nonmembers) for a Live Webinar, $49 for ISPE Members ($149 nonmembers) per Recorded Webinar, and $149 for ISPE Members ($199 nonmembers) for each Online Course, ISPE Online Learning is a viable alternative to education-related travel.

Training a group of employees at once is another convenience. ISPE welcomes webinar purchasers to share a live or recorded event with as many colleagues as possible. This can be done by gathering a group in a conference room or common area and broadcasting a webinar via laptop and projector.

Lists of upcoming live webinars, online registration, and a catalog of all ISPE recorded webinars are available at www.ISPE.org/onlinelearning.

Architects, Engineers – Constructors

CRB Consulting Engineers, 7410 N.W. Tiffany Springs Pkwy., Suite 100, Kansas City, MO 64153. (816) 880-9800. See our ad in this issue.

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.

Cleanroom Products/Services

AES Clean Technology, 422 Stump Rd., Montgomeryville, PA 18936. (215) 393-6810. See our ad in this issue.

Dust Collectors

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

Employment Opportunities

Validation Specialist

SNC-Lavalin, Inc. seeks a Validation Specialist to test pharmaceutical equipment on various projects based out of Exton, Pennsylvania. Bachelor of Science in Mechanical Engineering required. Two years experience in job offered or in molecular science and/or biochemical research required. Travel to client facilities is required. Fax resume to HR Manager at 610-524-2443.

Employment Search Firms

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

Instrumentation

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

Passivation and Contract Cleaning Services

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

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

Processing Systems

GEA Process Engineering, 9165 Rumsey Rd., Columbia, MD 21045. See our ad in this issue.

Rupture Discs

Fike Corp., 704 SW 10th St., Blue Springs, MO 64015. (816) 655-4546. See our ad in this issue.

Sterile Products Manufacturing

Process Tek - *Sterility by Design*
INNOVATION, RELIABILITY & PROFESSIONALISM
R&D, Validation, GMP Auditing,
HACCP, Problem Solving and Training
for sterile products, packages & processes
Kailash S. Purohit, PhD
www.processtek.net • kaipurohit@processtek.net

Tanks/Vessels

Lee Industries, PO Box 688, Philipsburg, PA 16866. (814) 342-0470. See our ad in this issue.

Validation Services

Commissioning Agents, Inc., 1515 N. Girls School Rd., Indianapolis, IN 46214. (317) 710-1530. See our ad in this issue.

Valves

Gemu GmbH & Co., Fritz-Mueller-Str. 6-8, D-74653 Ingelfingen, Germany. +49 7940123-0. See our ad in this issue.

Water Treatment

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

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

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

JIM CRUMPLEY & ASSOCIATES
Pharmaceutical Recruiting Specialist
Put our expertise to work for you in:

- Facilities
- Process
- Automation
- Project
- Validation
- Quality Engineering

1200 E. Woodhurst Drive, B-400 • Springfield, MO 65804
Phone: 417-882-7555 Fax: 417-882-8555
E-mail: recruiter@crumpleyjobs.com
Web site: www.crumpleyjobs.com
We've been getting results since 1977!

Now Available!

ISPE
2010 Global Media Planner

For advertising, exhibit, and sponsorship opportunities, call ISPE Sales Executive, North America, Dave Hall at +1-813-960-2105.

ISPE ENGINEERING PHARMACEUTICAL INNOVATION

2008-2009 *Pharmaceutical Engineering* Article of the Year Finalists

We are pleased to announce the 2008-2009 Roger F. Sherwood Article of the Year Award Finalists. The winner will be selected from this group and recognized at ISPE's 2009 Annual Meeting.

September/October 2008, Volume 28, Issue 5
Functional Safety in the Life Science Industries
by David Hatch, Iwan van Beurden, and Eric W. Scharpf

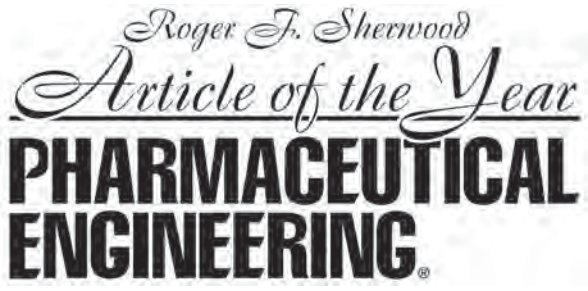
November/December 2008, Volume 28, Issue 6
Evaluation of Electron Beam (E-Beam) Sterilization Technology for Filling of Drug Products in Pre-Filled Syringes (PFS)
by Xiaogang Pan, Xiangning Deng, Michael Lee, Thomas O'Sullivan, Edwin Torres, Adrian Distler, and Narinder Singh

January/February 2009, Volume 29, Issue 1
Online Total Organic Carbon (TOC) as a Process Analytical Technology for Cleaning Validation Risk Management
by Keith Bader, John Hyde, Peter Watler, and Amber Lane

March/April 2009, Volume 29, Issue 2
PAT and Green Chemistry: The Intersection of Benign by Design and Quality by Design
by Dr. Berkeley W. Cue, Dr. John Berridge, and Julie B. Manley

May/June 2009, Volume 29, Issue 3
The FDA's Draft Process Validation Guidance – A Perspective from Industry
by Nuala Calnan, Alice Redmond, and Stan O'Neill

July/August 2009, Volume 29, Issue 4
Amplified Media Circulation – A New Way for Enhanced Sterilization Cycles
by David A. Karle, Gerald McDonnell, and Teppo Nurminen



more than engineering

"Vaccines are one of our industry's most critical tools for improving the world's health. I know how to make a difference by using my knowledge to help customers all over the world design vaccine production facilities which are flexible, optimised, and in compliance."

/ Klaus Hermansen

Klaus Hermansen

- International senior vaccine expert and top designer
- 25 years of experience in vaccine manufacturing and engineering

Special competences:

- Front end services and basic design
- Process and facility design
- Regulatory issues and workflow design

Consulting | Engineering | Construction | Validation | Solutions

To succeed in today's market, you require a focused partner created from industry DNA who can deliver a competitive advantage.
For more information on our vaccine know-how, please write to
contact@nnepharmaplan.com

nne pharmaplan®

nnepharmaplan.com