PHARMACEUTICAL ENGINEERING®

THE OFFICIAL TECHNICAL MAGAZINE OF ISPE

MAY/JUNE 2014 VOLUME 34, NUMBER 3

Good Distribution Practices

JIT and E-Labeling

Disposables Technology

Risk Mitigation

Transfer Station Design

Managing Risk

Student Poster Winner

Connecting a World of Pharmaceutical Knowledge

ISPE®

www.PharmaceuticalEngineering.org

GENERAL VENTILATION

TABLET PRESSES

GRANULATING

TABLET COATING

FILLING & PACKAGING

MIXING & BLENDING

LOCAL EXHAUST

DRYING

CENTRAL VACUUM

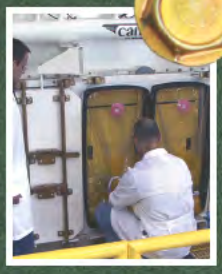
AND MORE

DUST PROBLEMS SOLVED

Farr Gold Series® Industrial Dust Collector

Safely and Economically

Bag-In Bag-Out



Scan QR Code, Place Phone Here

Turn your phone into a window to actually see inside the Farr Gold Series.

KS LIKE A SAFE BECAUSE IT'S

BUILT LIKE A SAFE™

877-749-8664 www.camfilapc.com

camfil
AIR POLLUTION CONTROL

editorial staff

PHARMACEUTICAL ENGINEERING®
(ISSN: 0273-8139) is published bimonthly by ISPE, 600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609, USA. Telephone +1-813-960-2105. Fax +1-813-264-2816. Periodicals postage paid at Tampa, Florida, USA.

subscriptions

US Postmaster:
Send change of address to *Pharmaceutical Engineering*, 600 N. Westshore Blvd., Suite 900, Tampa, Florida 33609.

Canada Postmaster:
Send change of address information and blocks of undeliverable copies to PO Box 122, Niagara Falls, ON L2E 6S8. Canada Post Agreement Number 40012899.

www.PharmaceuticalEngineering.org

ISPE Global Headquarters
600 N. Westshore Blvd.
Suite 900
Tampa, Florida 33609 USA
Tel +1-813-960-2105
Fax +1-813-264-2816
ask@ispe.org

www.ISPE.org

INNOVATION

In 2013, IMA invested 37 million Euros in Research & Development and had over 80 patent and design applications filed.

Technological innovation is the key to achieving global goals such as food waste reduction and better access to more effective drugs.

Numbers are important.
Especially when you figure them out.

IMA SPA
Sustain Ability

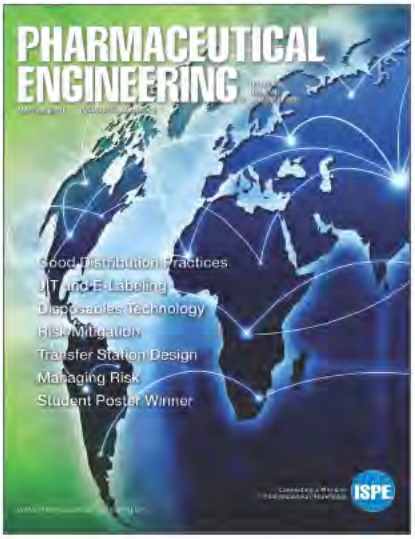
www.ima.it

table of contents

PHARMACEUTICAL ENGINEERING®

THE OFFICIAL TECHNICAL MAGAZINE OF ISPE

MAY/JUNE 2014
VOLUME 34, NUMBER 3



Insight to Operation

People | Process | Product

commissioningagents.com

Contact:		
USA Southeast	e: Jennifer.Clark@cagents.com	c: +1 919 696 2335
USA Northeast	e: Stella.Lanphear@cagents.com	c: +1 203 482 2757
USA Midwest	e: David.Shenberger@cagents.com	c: +1 317 721 9847
USA Mountain	e: Tony.Thompson@cagents.com	c: +1 970 978 0485
USA Pacific	e: Nicki.Lange@cagents.com	c: +1 215 237 5127
Canada	e: Reid.Jenner@cagents.com	c: +1 403 809 8078
Puerto Rico	e: Vimarie.Vega@cagents.com	c: +1 787 410 4682
Europe	e: Alice.Redmond@cagents.com	c: +353 86 8385088
Asia	e: Belinda.Braggs@cagents.com	c: +65 9115 2580
China	e: Lissa.Ji@cagents.com	c: +86 13817128872

USA | Canada | Puerto Rico | Europe | Asia

Welcome to this edition of *Pharmaceutical Engineering* where the focus is on complexity and risk in the global supply chain. One feature article asks how strategic planning helps to mitigate risks in the pharmaceutical supply chain, and another article explores patient-centric innovations in the clinical supply chain.

The continuing evolution of industry in response to such ever-changing technical, economic and regulatory demands provides many opportunities for the Society to serve Members, their companies and regulators as their authoritative resource for information and dialogue on scientific, technical and regulatory best practices.

To better serve our readers, *Pharmaceutical Engineering* has introduced eight *new departments*, reflecting the dynamic and complex nature of our industry.

Facilities and Equipment case studies illustrate how the selection of process equipment and the design of facilities and support utility systems can consistently deliver the critical physical and chemical requirements of drugs products.

Information Systems articles report on the different types of data management systems that are integral to successful drug development, manufacturing and distribution, as well as the system life cycle model, quality assurance practices, and the controls necessary to maintain data integrity and security.

Product Development articles explore the interactions of multidisciplinary functions and the scientific application of experimental design methodologies and explain a process to reproducibly and economically manufacture a product.

Production Systems articles demonstrate the full range and scope of unit operations and production steps for manufacturing APIs, the building and critical process utility systems that support the manufacturing process, as well as the means of managing and dynamically controlling, and automating manufacturing and warehousing operations.

Quality Systems articles focus on the role and elements of a quality management system and its impact within the overall risk management approach, as well as its implementation in a scientific and pragmatic manner.

Regulatory Compliance articles highlight international regulations and guidance issued by regulatory bodies and coalitions which shape the world's current pharmaceutical-related requirements and future directions.

Research and Development articles illustrate research methods and results describing new and innovative methods and techniques, including manufacturing and applied pharmaceutical science and technology, process and product understanding and control.

Supply Chain Management articles feature the key components and financial impact of supply and distribution chains.

Pharmaceutical Engineering is playing its part in achieving ISPE's vision and goals, as the Society aims to be the leading technical organization for professionals engaged in producing quality medicines and pharmaceutical devices globally, across all sectors and functions.

We believe that the new departments and this organization of information in *Pharmaceutical Engineering* will help ISPE meet these goals.

As always, I welcome your feedback – email me at ghall@ispe.org.

Gloria Hall
Editor, *Pharmaceutical Engineering*

Pure Fristam.

FKL
Positive
Displacement
Pump

For decades, Fristam has set the standard for reliable, efficient, high-purity centrifugal pumps. Our FKL PD pump is built with that same Fristam quality, to provide gentle product handling and consistent flow.

As with all our pumps, it comes with the best service and most comprehensive documentation in the industry. Let the proven performance of Fristam ensure the security of your process. There is a reason you've trusted us for so long.

Fristam PUMPS®

Engineered For Lasting Performance®

www.fristam.com/fkl

ISPE – Your Most Strategic Career Asset

Berg discusses how ISPE is helping Members gain knowledge and exposure to new ideas, methods and perspectives through a wide array of programs, activities and publications.

Is it just me?

When did the world become so complex? Since when (or how) did communication, presentation and financial skills or my understanding of other cultures and leadership tactics become "as important" as my technical or functional contributions? It is just me or are others also performing one, two or even three jobs simultaneously and permanently connected to their electronic devices? Does every company expect this much of their employees?

Wow. If you have asked yourself any of these questions lately, you are not alone. The good news is that ISPE can help you navigate through increasing company demands and faster-paced environments as well as the barrage of information on regulatory and engineering trends, new technology and global good practices.

The key to success is to never stop learning and know that your most strategic career asset is ISPE. In most companies, being a technical or a subject matter expert is no longer enough. Today, most companies require "us" to be subject matter and functional experts as well as "generalists" familiar with many business areas. ISPE understands these career trends and is helping Members gain knowledge and exposure to these new ideas, methods and perspectives through a wide array of programs, activities and publications. The power of knowledge combined with a diverse ISPE network of peer resources offer insight that will help lead you to success.

A key benefit of active Membership involvement is exposure to peers and experts who work outside of your immediate team and have experiences and opportunities to share. Getting involved in ISPE Affiliates, Chapters and Committees can connect you to peers, industry leaders and regulators with information on new technology, compliance and quality trends and beyond. It was a privilege to meet Members during the ISPE China's Spring Meeting in Shanghai, China in April. At this meeting, 600 Members gathered to hear speakers from China, the Asia-Pacific region, Europe and the US discuss regulatory, compliance and technical issues while enhancing the knowledge of local Members and their companies. Similarly, ISPE's European Conference addressed issues and trends relevant to the unique European regulatory environment.

ISPE will host three concurrent US events during ISPE's first annual Pharmaceutical Quality Week, 2-5 June in Baltimore, MD. In addition to education on hot topics, ISPE's Pharmaceutical Quality Week celebration will recognize ISPE Members' commitment to quality in the production of innovative and reliable medicines. This week also features the 3rd Annual ISPE-FDA CGMP Conference, the new ISPE-FDA CMO Executive Workshop and ISPE's new Facility of the Year Awards Banquet honoring this prestigious award's category winners. During the week, attendees will discuss, for example, data integrity, reliable supply, supplier relationships, and compliance and quality systems while also networking to learn what is happening throughout the industry. These events also offer expert technical and leadership perspectives that will enhance your understanding of the issues surrounding drug shortages, quality metrics and breakthrough therapies and how they affect you. I encourage you to take advantage of the ISPE global and local programs offered in your area.

Increase Your Pharmaceutical Knowledge and Skill

7 *Irresistible* Reasons to Join ISPE Today!

1. Increased Knowledge
2. Enhanced Connections to Colleagues Near and Far
3. Exchange of Information With Peers Around the World
4. Expanded Learning Opportunities
5. Career-Boosting Exposure for Industry Newcomers
6. Accelerated Career Advancement for Seasoned Professionals
7. Member-Only Savings

"We strongly encourage colleagues to participate in ISPE education and training programs to build the capability necessary to keep the network and Pfizer competitive."
—Chaz Calitri, VP Pfizer Global Engineering, Pfizer, USA

"It is very convenient to be able to learn at your desk, at your own pace using ISPE e-learning courses."
—Bernadette De Leye, Quality Excellence Coach, STEXCON, Belgium

"ISPE provides a fantastic platform for pharmaceutical professionals to communicate and exchange ideas, practices and experience."
—Henry Yuan, Pharmaceutical Engineering Postgraduate, Tianjin University, China

ISPE Connecting a World of Pharmaceutical Knowledge

Join Today! ISPE.org/Join

A Changing Landscape: Perspectives on Temperature Management for the Distribution of Non-Refrigerated Clinical Supplies

by Dr. Nicole Assfalg, Ted Bradley, Tim Brewer, Sébastien Delporte, Kristen DeVito, Bruce Guenter, and Patricia Thomas

This article discusses the shipment of room temperature products from several perspectives: the changing regulatory environment, risk assessment and mitigation, new technologies and budgetary pressures.

This article was created through joint collaboration and authorship from several subject matter experts in clinical supply chain and quality operations. The collaborative approach for this article was purposefully designed to provide readers with diverse perspectives from a cross section of industry organizations and their respective functional operations.

The need for a thorough temperature sensitive shipment program which incorporates room temperature products will prove invaluable to your clinical research supply chain. Pro-actively anticipating and planning scenarios where clinical trial products can face the risk of quality degradation needs focus within your clinical supply chain. This article will discuss shipment of room temperature products from several perspectives: the changing regulatory environment, risk assessment and mitigation, new technologies and quality and budgetary pressures. It's our hope that it provides additional perspective and insights that enable those charged with managing clinical supply organizations the opportunity to strengthen their management of logistics programs for room temperature products.

Regulatory Environment

There's no question that one of the principal drivers with respect to room temperature shipment management is the surge of new regulations related to Good Distribution Practices (GDP). Several countries have recently issued guidances or new regulations that span beyond management of cold chain logistics and reach specifically into the room temperature arena. Perhaps the most widely recognized of these GDPs are those most recently issued by the European Union (EU).[1] There is still much debate about how best to apply the EU GDPs within clinical supply chain operations but there is little argument that this body of work reaches further into room temperature shipment management than any previous set of guidances.

The industry has long accepted cold chain requirements and has shipped products packaged accordingly. As our industry has gained considerable experience with the management of cold chain products and how to efficiently ensure quality and temperature control of cold products, we see regulatory bodies turn more focus to room temperature shipments. This is supported by the implementation of similar regulations in many non-European countries. Issuance of GDPs and other regulations in countries such as Canada, Japan, China, and Israel along with several other emerging markets have made room temperature shipping a business practice to be addressed.

Not unified by chance. Unified to enhance.

We are a partnership of companies, a team of talented professionals, an alliance of like-minded individuals; all strategically unified to better suit the needs of our customers. By combining our vast skillsets with our superior expertise, we have the power to change the way you think about service. Together, anything is possible.

Azzur Group LLC
AZZURGROUP.COM

Azzur Labs LLC
AZZURLABS.COM

Azzur Engineering LLC
AZZURENGINEERING.COM

BIOMaintenance SERVICES
BIOMAINTENANCESERVICES.COM

Find out more at:

CHANGEISCOMING.CO

726 Fitzwatertown Rd. • Suite 6 • Willow Grove, PA 19090 | 610.363.0422 | www.azzurgroup.com

Inc. 5000

PINNACLE GLOBAL ISPE PROGRAMME SPONSOR 2014

Highlighted below are a few key elements of the EU-GDP, as they relate to distribution:

- It is the responsibility of the supplying wholesale distributor to protect medicinal products against breakage, adulteration and theft, and to ensure that temperature conditions are maintained within acceptable limits during transport.
- Regardless of the mode of transport, it should be possible to demonstrate that the medicines have not been exposed to conditions that may compromise their quality and integrity.
- Risk assessment of delivery routes should be used to determine where temperature controls are required. The selection of a container and packaging should be based on the storage and transportation requirements of the medicinal products; the space required for the amount of medicines; the anticipated external temperature extremes; the estimated maximum time for transportation including storage at customs; the qualification status of the packaging; and the validation status of the shipping container.

So with all the all the new GDP guidances and regulations being issued driving industry to improve temperature sensitive shipping programs for room temperature products what is one to do? Where can you start if you need to strengthen your program?

Risk Assessment

If you haven't already, consider starting with the development of a "risk assessment" specifically for shipment non-refrigerated research products. There are a number of approaches that your clinical supply chain organization could utilize to build one or augment an existing cold chain risk assessment to fit your needs. As with any good risk assessment your clinical supply chain should ensure your key partners are invited and encouraged to help build the risk assessment criteria and cross functionally develop responsibilities that each key partner will play within your organization. For example, the inclusion of your quality assurance and analytical/stability organizations could ensure critical hand offs and procedural steps are not missed when examining temperature excursions post shipment. Capturing feedback and recommendations from key experts across your research organization for inclusion in your risk assessment should enable your logistics organization to expediently resolve issues when they occur out in the field.

As mentioned above, a risk assessment can be developed in a multitude of ways with no single framework being superior. However, when considering a risk assessment targeted at shipment of room temperature products there are certain criteria that will likely be more central to its success. Key elements to consider should include:

- How the organizations stability program is structured and what tolerances the program can afford products in general. Further assessment can be taken with respect to individual product configurations (e.g., liquids, lyophile, or solid oral) and whether they are internally manufactured or purchased.
- The organizations current shipping program and what type of shipping materials the organization are able to leverage (e.g., insulated shippers, conventional thermal bricks, phase change materials, etc.)
- The geographic range a product may need to ship along with seasonality.
- Mode of transport, estimated maximum time for transportation, with inclusion of customs clearance.

All of these factors can be used to help your organization determine the level of protection required when shipping room temperature products. Should temperature monitors be employed? Should insulated packaging be used? Perhaps both.

For example, after completing a thorough risk assessment, an organization may find that a product's stability profile is very stable and aligns with the ambient temperatures of the transportation route and thus a less expensive (robust) shipping container may be used with success. The value of the product and the cost of average shipment should be considered when determining the appropriate protection and monitoring of the shipment. A universal shipping system that applies a "one-size-fits-all" solution to all climatic zone, seasons, and transportation routes may be overkill for a product that is stable and in ready supply or likewise not sufficient for products in your portfolio with less than ideal stability data from a logistics perspective.

The benefit of developing a robust risk assessment is that it enables your organization to leverage a consistent and scientifically based methodology for how you arrived at a planned method of shipping clinical supplies to patients. The results of such assessments can further be used to justify changes in technology and materials used within your temperature sensitive shipment program.

Technology, Devices and New Developments in Shipping Materials

As mentioned previously, the regulatory landscape is changing and incorporating room temperature shipments into an existing cold chain program or developing a distinct room temperature monitoring program within your clinical supply organization will help ensure your organization is prepared to meet the challenges that lay ahead. Training your organization to view room temperature shipments the same way we presently view cold chain shipments will make companies and clinical supply chain vendors better prepared to manage changing regulatory expectations. With emerging regulatory

THE WORLD LEADER IN CLEAN AIR SOLUTIONS

Even after
90 years,
we continue
to raise the bar.

AAF...redefining air filtration

Just when you thought the bar had been set,
WE ARE RAISING IT.

aafintl.com

Better Air is Our Business®

AAF® INTERNATIONAL

requirements, technology will play an integral role in ensuring temperature stability and data transparency while in transit.

Regardless of whether your program drives the use of data loggers or not, practical applications of technology and careful planning can deliver benefits such as reduced delays in the supply chain, supportive data for temperature excursion queries, quicker decision making at depots and investigational sites.

Temperature monitoring becomes important under the following conditions:

- If adequate data on the stability of the product is not available
- The events that may cause temperature excursions are unknown and no other means can be employed to detect them
- If the product is required to undergo multiple hand-offs and the distribution lane may expose the product to excessive vibration, shock, pressure, and/or temperature extremes

In cases where data loggers are employed for room temperature shipments, firms can take advantage of improved shipment traceability. The use of data loggers provide not only valuable temperature data, but when paired with newer innovative service offerings such as data trending applications, firms can also help utilize the data to extract other valuable information such as:

- More precise handling times (post proof of delivery)
- Better control on shipment receipts at clinical sites through exception management of temperature monitor data reports

Variation is expected, but monitoring and comparing relative performance of room temperature shipments moving within the same lanes or from different origination points helps an organization identify when further investigation may be warranted.

Distribution lane performance can be measured in terms of number of deviations from the specified temperature range against the number of times the shipment was delivered successfully on a particular distribution lane. It can be monitored to identify situational or systemic issues in that distribution lane. Utilizing temperature monitoring data to trend unexpected shifts in temperature conditions during transit can be very valuable. These exceptions can be compared to handoffs in the transit lanes to identify undesirable gaps in service such as handoffs between carriers and brokers, delays in final delivery and other unexpected issues.

Temperature monitoring data also can be utilized to gather information regarding receipt practices at clinical sites and intermediate depots/warehouses. Delays in deactivating the temperature monitors may provide insights into potential needs for additional site personnel training. While this may be more critical for cold chain products, the value of this information for room temperature shipments cannot be overlooked. Helping receiving sites understand the importance of promptly turning off temperature monitors and moving products into the appropriate controlled storage locations can reduce the occurrence of post-delivery loss of products at the final destination. Losses at final destination can be particularly difficult when patient dosing cycles may be impacted.

New Technologies

New advancements in data logger technology include USB functionality that enables quicker and easier data transmission directly to personal computers. Additionally, data loggers now have the capability to provide multiple alarms, capturing both labeled temperature and stability data ranges through email, and smart phones. They also support web access for graphing, reporting, and configuration features online.

Looking farther out, there is emerging technology that combines Global Positioning Systems (GPS) functionality with conventional temperature monitoring capabilities and advanced messaging services to provide real time location and temperature of products while in transit. While these technologies are not mainstream yet, it is worth noting that these devices are becoming available more and more, and their costs continue to decrease as manufactures introduce these products into the marketplace.

The shipment of room temperature products is an area of growing interest for the manufacturers of passive shipper systems as well. Advanced phase change materials can be used in room temperature designs since they phase at very precise temperatures - *Figure 1*.

Advancements of Phase Change Material (PCM) allow passive containers, along with Vacuum Insulated Panels (VIP), to sustain controlled room payload temperatures for longer

Figure 1. RePak120 room temperature™ insulated pallet shipping container for room temperature shipping.[2]

periods of time. Compared to water-based solutions, PCM containers offer superior performance for both domestic and international shipments. They offer consistent distribution of temperature throughout the payload, eliminating hot/cold spots and greatly reducing the potential for costly temperature excursions. Using PCM passive containers also eliminates the need for adding gel packs or additional packaging material, which translates into larger usable payload space and lighter tare and dimensional weight. This efficient design of the container means that fewer containers are needed per shipment. Additionally, a smaller and lighter container results in a lower cost per shipment. In addition to transportation savings, labor savings can be realized with a simpler and quicker pack-out process. Unlike other passive systems, PCM technology typically requires only one conditioning method and a single pack-out for all climatic zones and seasons.

By designing temperature assurance packaging systems with a 20°C or 23°C phase change material, companies can increase the likelihood the product payload stays within the required 15°C to 25°C for the duration of the shipment. Conversely, if a water-based refrigerant is used, a greater amount of refrigerant is typically required to buffer the product against freezing. This results in larger and heavier shippers with a greater number of components to assemble, which is costly and cumbersome at both the origin and destination site. Leading packaging companies are developing new insulation materials to provide the high level of performance required for room temperature shipments while potentially decreasing the total cost of ownership by making smaller and lighter shippers with fewer required refrigerants. An insulated shipping system's total cost should not just be based on the purchase price. Other costs such as number of components to be stocked, time and labor to assemble the system, and cost to ship should also be factored in.

Returnable versus Single-Use Container Comparisons and the Impact on the Environment

When considering passive shippers, environmental impact is becoming a factor in the shipper selection process. As companies consider social responsibilities, the option to offer reusable shippers as part of the packaging solution is gaining momentum. Conducting a cost benefit analysis that compares single use to reusable containers may result in both shipper and freight cost savings, as well as an overall lower cost per use by choosing a reusable container. Although there are many variables to consider, a typical reusable container could potentially pay for itself after five to seven uses in some circumstances. A reusable solution can also have a major impact on reducing the carbon footprint. A recent study concluded that using a multi-use solution, compared to a single use approach, over a course of 30,000 shipments, could reduce global warming potential by 75% and postconsumer waste by 95%.

Thermal protection packaging solution providers offer services and technologies for reverse logistics planning and support, enabling the return of shipping containers through clients' transportation providers. They keep a track of the logistics for each container and provide alerts for key milestones. The containers are inspected, decontaminated, and refurbished and when required, components are replaced.

Cost and Quality

The costs associated with developing a robust temperature sensitive shipping program for room temperature products should not be overlooked. Costs associated with the additional labor and time to pack shipments, use of temperature monitors, increased material cost of insulated containers and packing materials as well as higher transportation costs due increased container sizes and weights can increase the cost of your room temperature shipments. Additional direct and non-direct expenses to consider are identified below.

- **Direct Costs**
  - Supply chain mapping (shipping lanes, methods) and qualification of shipping containers/systems
  - Management and tracking of temperature monitors, data (trending) and excursions
  - Increased labor infrastructure demands, and or service charges to warehouse and maintain additional shipping system components
  - Cost of delays due to interruption of supply and cost of replacement shipments resulting from catastrophic temperature excursions during shipment
- **Indirect Costs**
  - Resource to perform risk assessment and creation of SOPs and training; additional documentation requirements, record reviews, inspections, and verifications
  - Increase in vendor qualification requirements and insurance coverage
  - Environmental considerations of disposal

The potential cost impacts of expanding a temperature sensitive shipment program to routinely incorporate room temperature product may seem overwhelming at times. However, there are cost implications to not doing so as well.

As noted above, there are several aspects to take into consideration when developing a room temperature program and if not thoughtfully approached one can quickly find themselves overwhelmed. With the new technology becoming available logistics can become very sophisticated, but it may not be a value that it fully realized depending on the size and reach of your specific clinical supply chain. Likewise, your clinical supply chain may be geographically broad enough that you're subject to a wider array of regulatory expectations and challenging environmental conditions. Taking advantage of newer technology and services may return your investment more quickly by enabling you satisfy more conservative regulations and strengthening your physical logistics chain. Whichever circumstances you find yourself in clinical supply chain organizations need to consider a thoughtful and pragmatic approach to assessing those factors which could drive up costs and determine whether they make sense within their specific operations. Utilizing a team approach within your clinical supplies organization consisting of all the right stakeholders (quality, regulatory, analytical, supply chain, caregivers, and patients) to build your temperature sensitive shipment program will help ensure you avoid costly mistakes that will need to be addressed later on and set your organization on the right path for future growth as the clinical supply chain changes.

Demonstrating the benefits of a robust temperature management program that encompasses all the products that your organization ships will demonstrate quality and control within your clinical supply chain logistics operations. Having these controls in place and being able to articulate expectations and requirements upfront will help reduce concerns or questions from patients, caregivers, and regulators during the course of clinical trials. And when we stop to think about it, that's what it is all about, making sure patients benefit from the life changing medications we deliver to them.

References

1. *The new EU-Guideline on Good Distribution Practice (GDP) of Medicinal Products of Human Use* (2013/C 68/01), published 7 March 2013.

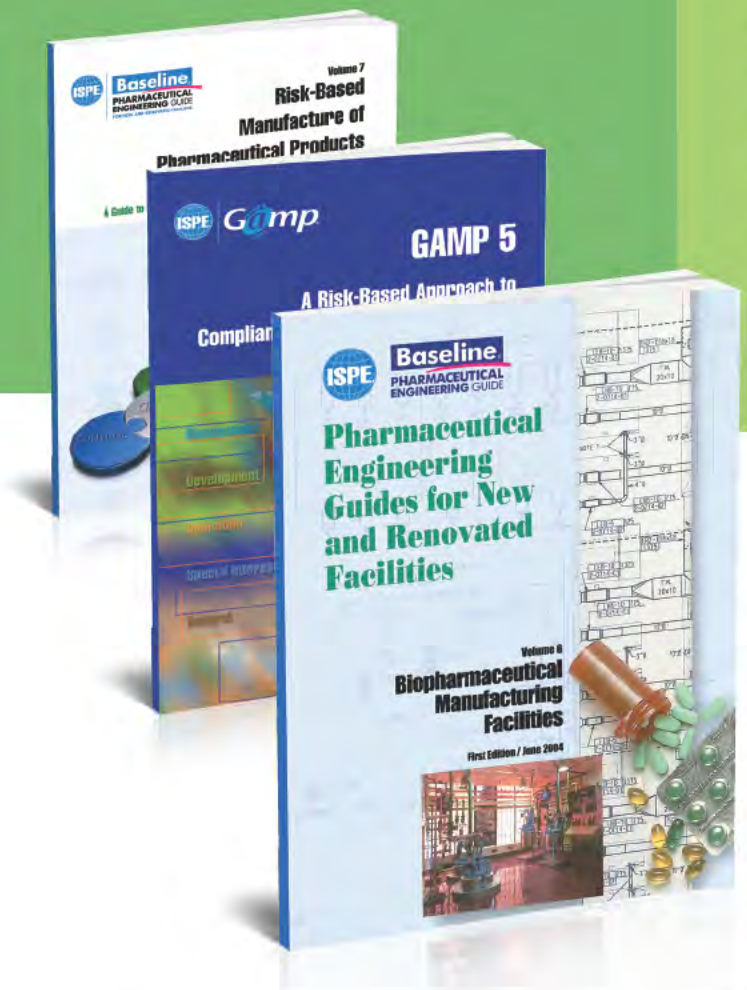
2. "Cryopak Introduces the RePak120CRT(TM) Insulated Pallet Shipping Container for Temperature Sensitive Shipping," PRWeb, 13 April 2013, http://www.prweb.com/releases/2011/4/prweb8302952.htm.

Authors

Dr. Nicole Assfalg, Head of IMP Quality Global Operations Europe – Distribution and Supply Chain, Hoffmann-LaRoche Ltd.
Ted Bradley, Sr. Director, Global Clinical Supply Logistics, Pfizer Inc.
Tim Brewer, President Global Clinical Supply Operations, Yourway Transport
Sébastien Delporte, Quality Assurance Logistics Manager, Eli Lilly and Company
Kristen DeVito, Global Director CSS Business Solutions, Catalent Pharma Solutions
Bruce Guenter, Director, Global Clinical Supply Logistics, Pfizer Inc.
Patricia Thomas, Sr. Clinical Supplies Program Manager Global Clinical Trial Supply Chain, Takeda Americas, Inc.

ISPE Guidance Documents

Your Source for Practical Solutions to Your GMP Challenges.



Visit www.ISPE.org/Store for more information.

Whatever problem you are trying to solve—achieve regulatory compliance, improve quality, increase efficiency, and/or reduce cost—ISPE has a document solution that fits your needs.

ISPE's series of documents offer practical answers to the complex, dynamic challenges facing facility designers today by addressing GMP as well as non-GMP issues.

Created in partnership with global regulatory authorities and pharmaceutical manufacturing industry experts, ISPE's Guidance Documents:

- Reflect current regulatory expectations and good practices
- Provide interpretation of regulatory standards
- Offer practical advice on regulatory initiatives
- Encourage innovation and technological advancement
- Provide effective, cost-efficient approaches
- Present information or advice on a particular topic area
- Explain underlying technical principles
- Suggest solutions in an area where no single answer is correct

Patient Centric Innovations in the Clinical Supply Chain

by Karen Gram, Hans Heesakkers, Roger Lauwers, and Sascha Sonnenberg

This article discusses the use of Just in Time (JIT) and E-labeling to minimize supply chain problems and increase the safety of subjects in a clinical trial.

The clinical supply chain is a supply chain within R&D, covering the manufacturing, packaging, labeling and distribution of investigational products to subjects participating in a clinical trial. Triggered by the desire to accelerate the R&D pipeline, the supply chain matured with revolutionary speed in the past decade. ISPE's Investigational Products Community of Practice (IP CoP) played an important role in this evolution and is now at the dawn of yet another innovation: e-labeling and JIT-labeling.

Clinical supply chains are often set up project by project and there is very little leverage of an existing supply chain infrastructure compared to the commercial supply chain. Where the commercial supply chain is challenged with country specific regulatory requirements, the clinical supply chain is challenged with regulatory requirements per country per study. As indicated in Figure 1, the total number of studies is increasing as well as the number of late phase studies (studies with a higher volume of medication kits).

Not only is the number of studies and the volumes of required medication increasing, the number of countries participating in a trial is also increasing - *Figure 2.*

Every added country to a trial multiplies the amount of challenges. When emerging countries are added to a trial, the amount of challenges multiply due to the lack of experience in setting up supply chain infrastructures in these countries.

Challenges in the Clinical Supply Chain

Demand uncertainty is the key challenge in the clinical supply chain. It is uncertain in which country the subjects in a trial are going to enroll and when and under which country specific conditions that country is going to allow that trial. Subject enrollment is a key success factor for a trial so trial managers plan to have an increasing overage of country specific stock available. Filling the supply chain with stock requires an early start. However, these early starts bring their own set of challenges, including the following:

- Regulatory approvals are still pending for usage of the new formulations.

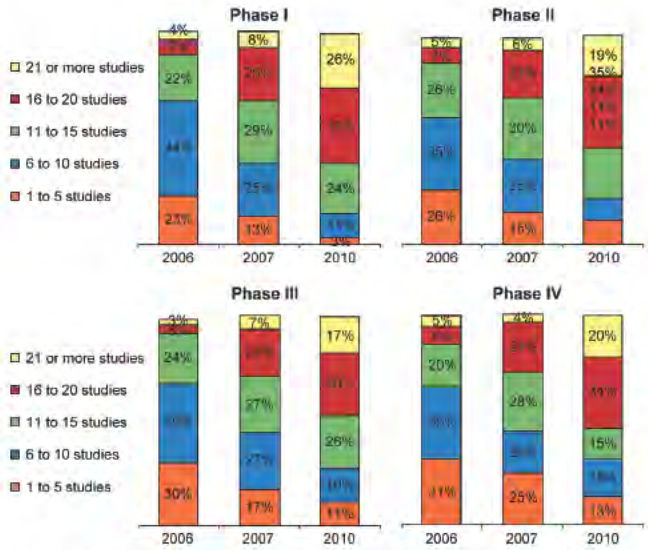


Figure 1. Figures from AMR research on the number of studies per phase.

There are many reasons to select the new BioPure LSX High Efficiency USP High Purity Water System

Two are **Clear.** Superior **Technology.** Low **Price.**

Guaranteed 24 Hour Turnaround Time On All Standard Quotes.

Mar Cor Purification Life Science Markets

• Pharma/ Medical • Cosmetics • Lab & Research • Beverage • Semiconductor

ISO 9001 & ISO 13485 Certified · US: 800-633-3080 · Canada: 800-268-5035

For more information email us at info@mcpur.com or visit www.mcpur.com

MAR COR® PURIFICATION
A Cantel Medical Company

- Expiry dates can be updated since stability testing is ongoing.
- Study protocol designs are still in draft, formulations and treatment groups might still be added and packaging design can change last minute.
- Traditional planning systems work with firm bills of materials and use backward planning tools from API to finished medication pack. In the clinical supply chain, not all materials are known at the start of a project which makes the planning extremely cumbersome.
- Covering supply chain uncertainties by making significant overage often is no option since the new product is still in scale up phase and there may be a shortage of API to manufacture the extra stock.

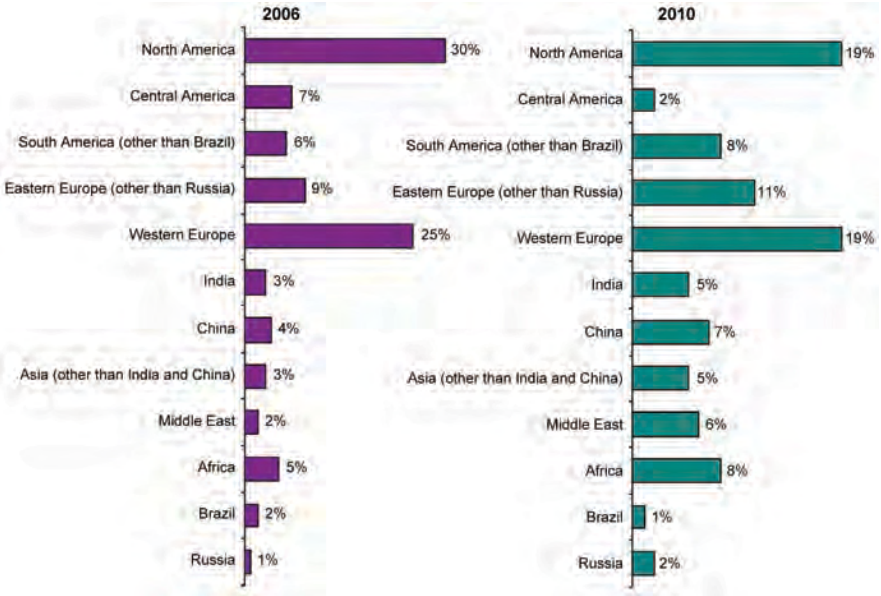


Figure 2. Figures from AMR research on the number of studies per region.

The sum of these challenges causes the clinical supply chain to be in a continuous "fire extinguishing mode."

Time, Stock and Kit Decoupling Point

To reduce these challenges, trial supply managers will strive during the setup of the trial supply protocol to bring the point where a medication kit becomes country specific as close to the patient as possible. The point where the medication kit becomes country specific is named the Medication Kit Decoupling Point (KDP). Figure 3 shows how it is possible to shift the KDP with different strategies.

Traditionally a medication kit becomes country specific when a label is attached to a primary pack. This eliminates all flexibility to late stage changes in participating countries.

Booklet labels on primary packs are a stack of different country specific labels attached to each primary pack. The technical challenges to design and produce these labels cause additional lead times and late changes to these labels often multiply this issue.

Untranslated primary labels are single language labels on a primary pack that might not be the language of the country the patient is in. Eudralex Volume 4 Annex 13 allows some possibilities for this in cases where "the primary packaging takes the form of blister packs or small units such as ampoules on which the particulars required in Paragraph 26 cannot be displayed" and where "administering the medication within a primary package together with secondary packaging that is intended to remain together, and the secondary packaging carries the particulars listed in Paragraph 26." However, local authorities not always allow untranslated labels on primary packs.

Booklet labels on secondary packs have the same challenges as booklet labels on primary labels. IP CoP has released a Good Practice Guide on Booklet Labels to reduce some of the disadvantages, but they remain to exist nevertheless.

Just in Time (JIT) labeling is the labeling of secondary packs per "ship-to-depot order" rather than per packaging order. This requires the release of a packaging batch to be split between packaging and shipping. A prerequisite for that is to design batch records in a way that the person who performs the release gets the right information at the right time and to reduce the work load of that person by either a higher degree of automation or by extending the resource capacity for this.

JIT labeling in depot is the labeling of secondary packs per "ship-to-site order" rather than per packaging order. This requires all that is required for JIT labeling and in addition the willingness of the person certified to release to out-

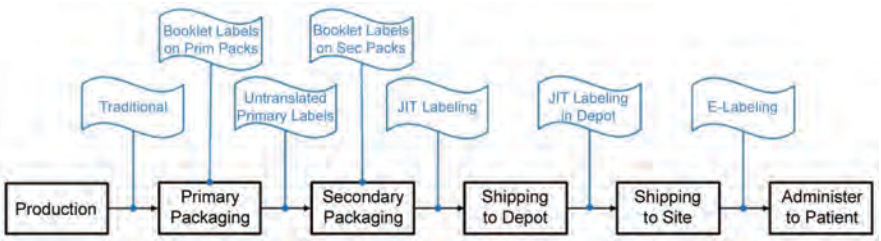


Figure 3. Medication Kit Decoupling Points (KDP) represented in the clinical supply chain.

Figure 4. Medication kit with E-Label being read by a mobile device.

source some of his activities to a counterpart in the depot.

E-labeling is the labeling of secondary packs with non-country-specific labels plus either a serialized barcode or a RFID chip. The bar-code or RFID chip will be read by a mobile device and upload the label in the patient's local language - *Figure 4*. Real time information on expiry date will be provided electronically. All information which is currently hand written on a label by the investigator (such as Subject ID, Investigator Name, etc.) will be automatically integrated on the e-label when the medication is provided to the patient.

What is E-Labeling?

Imagine you are a patient enrolled in a clinical trial and your mobile device would be the communication tool to retrieve information from your medication KIT. An acoustic alarm triggers you to take the medication. An App on the Smart device guides you to pick up the label (or insert) from a database in your own language. Another App provides a connection to specific instructions which are shown in a video (such as instructions for opening a child resistant package). You can be sure that the medication is not expired or has been recalled, because the device will provide the most up to date information and will warn you when changes occur.

You (or your caretaker) will be reminded if the medication intake did not occur according to schedule. The device will prompt you to provide your adherence behavior. Simply by touching your device to the patient KIT, the medication intake will be uploaded to the investigator site. The investigator can intervene if you missed a dose.

Suddenly you realize that you have forgotten to put your medication kit back in the refrigerator since the last administration. You go to the App on your device touch the medication KIT and receive an overview of the temperature excursion. The device shows you the temperature curve of the whole lifecycle of the medication kit. You will get an alert not to use the medication any more in case the temperature excursion has exceeded the stability boundaries - *Figure 5*.

Tomorrow is your appointment with the trial physician. During your visit, you will not be asked anymore how your held condition was at specific time periods since patient diaries and relevant questions were pushed to your device during the trial and you did answer these questions already - *Figure 6*. Likewise, the physician will not ask any more if you took the medication in time. All the data has been transmitted already by your mobile device.

While you fly over to the hospital tomorrow, your device will be on "in flight mode." The e-labeling App will still work and it will synchronize with your data with the central server once you go online again. If this sounds like "Star Trek" to you, be aware that the first prototypes of this already exist. It is using current technology and is robust enough to be validated.

Regulatory Prerequisites

Current regulations like Eudralex Volume 4 Annex 13 do not allow the replacement of label texts on paper labels with an E-label.

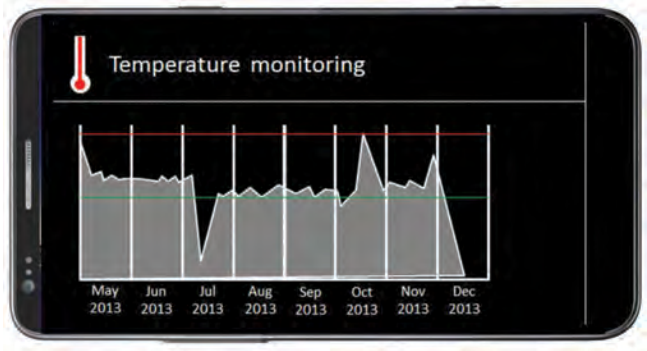


Figure 5. Temperature excursion graph on the E-label app.

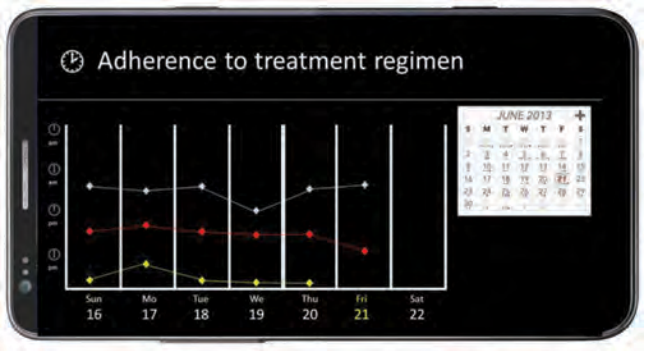


Figure 6. Graph of compliance with treatment regimen.

A new clinical trail directive for the EU is going to be published. The ISPE IP CoP wants to support implementation of the new clinical trial regulation.

For E-labeling, this requires "the industry" to be aligned and where possible start showing patient advantages. The objective of this article is to start mobilizing resources and budgets in the industry to allow this. ISPE IP CoP aims to be the platform to drive this regulatory shaping. Following is a list of topics to align on, but the topics are not limited to this list:

- Under which conditions are untranslated primary labels allowed?
- How should batch records be structured to allow JIT-labeling and E-labeling?
- How can QPs and other batch releasing persons operate within GxP while enabling JIT labeling and E-Labeling?
- How can the expiry date on an e-label overrule the expiry date on a paper label?
- Which guidance needs to be given to computer system validation of E-labeling systems?

This article is an invitation to connect to the authors and help shaping the clinical labeling future.

Is This the Final Solution?

Technology is an enabler. E-labeling will start a new era of possibilities that has yet to be discovered. The industry would not only improve on supply chain problems and increase the safety of subjects in a clinical trial, but also create the basis of new possibilities. Examples of that are:

- Anti-counterfeiting by uniquely identifiable packs and supply chain control on those
- Integration with PRO systems where patients keep their patient diaries in real time hence preventing the parking lot effect (FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims)
- Basing the expiry of a kit on the comparison of a stability profile with the temperature excursions of a kit rather than on an expiry date and the judgment of an individual
- Enabling E-labeling for the commercial supply chain

References

1. Eudralex Volume 4 Annex 13, *Investigational Medicinal Products.*
2. *ISPE Good Practice Guide: Interactive Response Technology,* International Society for Pharmaceutical Engineering (ISPE), First Edition, November 2011, www.ispe.org.
3. *ISPE Good Practice Guide: Booklet Labels,* International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2013, www.ispe.org.
4. AMR Research, "The Rx for Success in the Clinical Trial Supply Chain; A Time to Learn, Unlearn and Relearn,"18 February 2009.

About the Authors

Karen Gram has 40 years of industry experience and 25 years of experience in clinical supplies. She is a member of the ISPE Investigational Products CoP. Gram has successfully coordinated the production of the ISPE Good Practice Guides on Booklet Labels and IRT Systems. She can be contacted by tel: +45 3079 1614 or email: kgm@novonordisk.com.

Hans Heesakkers has 25 years of industry experience and 11 years of experience in clinical supplies. He is an active member of ISPE Investigational Products CoP and CS, ForumTechnology opinion leader for CTSM solutions. He can be contacted by tel: +49 175 57 64001 or email: hans.heesakkers@accenture.com.

Roger Lauwers has 37 years of industry experience and 30 years of experience in clinical supplies. He designed and implemented many innovative CTSM solutions as well as the prototype of an e-labeling solution. He can be contacted by tel: +3214602487 or email: rlauwers@its.jnj.com.

Sascha Sonnenberg has 15 years of industry experience and more than 10 years of experience in clinical supplies. He is a member of the ISPE Investigational Products CoP EU SC and was an active member of the Booklet Label Good Practice Guide Task Team. He has broad experience in label/labeling as well as storage and distribution of clinical supplies. He can be contacted by tel: +49 171 2635644 or email: sascha.sonnenberg@marken.com.

PHARMA EXPO™

Processing & Packaging Conference and Tradeshow

November 2–5, 2014 • Chicago, Illinois USA

JOINT VENTURE

PMMI ISPE

Smart Solutions for Lifecycle Innovation

At Pharma EXPO, meet solutions providers who understand the importance of controlling the integrity of your product throughout its lifecycle. Discuss your challenges with experts who know how the industry's systems work. Take away smart approaches to production so you can meet your goals for yield, performance, safety and security—from start to finish.

Register today at pharmaexpo.com

Co-located with:

PACK EXPO® ADVANCING PROCESSING AND PACKAGING

Change Notifications for Single Use Components: Criteria from an End User Perspective

by Sally Kline, Ekta Mahajan, Darrell Morrow, Bob Steininger, Nancy Sweeney, and Russell Wong*

*All authors contributed equally to this article.

This article presents science and risk-based approaches to categorize levels of changes in Single Use Systems (SUS) raw material and manufacturing processes.

Polymers are the materials of choice for the fabrication of SUS used in biopharmaceutical manufacturing. These polymers, typically plastics, elastomers or rubbers, meet bioprocessing demands by being lightweight, flexible, transparent, easily transportable, and durable. They also offer distinct advantages over fixed cleanable systems by decreasing expenses for building or modifying facilities, equipment cleaning, cleaning validation, and operations. Use of SUS also can considerably reduce changeover time between products.

The polymers used to construct SUS are synthetic and can be altered by heat, light, oxygen or sterilizing irradiation. Depending on the conditions and time of exposure, these changes may induce physical or chemical degradation. Discoloration, cracking or changes in the macroscopic mechanical properties of the polymers are obvious signs of degradation; however, degradation induced changes also can occur in polymers prior to visual detection. Key properties of the polymer including the Extractables and Leachables (E&L), gas transmission and/or permeability could be altered and detection requires analytical techniques.

To minimize the potential for polymer degradation, commercially available polymers typically contain specially formulated stabilizing additives. The additives are incorporated into the polymers to reduce degradation during the melting and forming of the polymer into the film or component, the sterilization process, shipping, and warehouse shelf life of the final assembled SUS. However, these additives that stabilize the polymer also may contribute to E&L that can impact the manufacturing process, quality, and of the drug(s) being manufactured.

Changes to the SUS manufacturing process or raw material used in their production can affect the physical and chemical properties of the polymers, and must be carefully evaluated prior to implementing the change. Biopharmaceutical manufacturing processes can be impacted by SUS manufacturing or raw materials changes that may initially appear insignificant.

To assist in the risk assessment, change notifications should include information that an end user can utilize to better evaluate the impact of the change through the company's change control program. Changes in the polymer type, additive package, film or component manufacturing process, sterilization, shelf life and gas transmission and/or permeability are many of the things that need to be assessed to determine the potential impact on the polymer properties and E&L.

For end users, this document provides a guidance on those issues to consider when assessing the severity of the change.

Predictable.

We honor your schedule.

Delayed departures, late arrivals, change of plans - we have all experienced how frustrating it is when we have important meetings and deadlines to keep!

In our industry it's vital to keep schedules – to get your new pharmaceutical manufacturing facility up and running on time, to ensure your critical process systems perform as specified and you are able to satisfy your commitment to the patients dependent on life saving therapies.

Pharmadule delivers solutions, from concept design through start-up and qualification. Our predictable and well-proven delivery model, based on our modular concept and off-site construction, will ensure the success of your project – meeting the market demand and maximizing your return on investment.

For us it's a matter of honoring deadlines – continuing to deliver the values that Pharmadule has been recognized for over the last 25 years.

On Time , On Budget - The Modular Way

pharmadule

www.pharmadule.com

Depending on the severity of the change, this document can provide information for the supplier to identify the relevant time and resources an end user will need to assess the changes as well as repeat studies if necessary before the changed material can be safely utilized in the manufacturing process.

Supplier Product Change Control Criteria

A number of product changes occur during the life cycle of any raw material, including SUS, used in the production of biopharmaceuticals. The impact of these changes is assessed by both the supplier and end users to identify the risk of impact to patient safety and manufacturing process. The transparency of the technical exchanges between the end users and supplier and their supply chain is critical to develop the understanding of the science and data driven risk assessments.

Industry best practices do not exist currently to support the evaluation or assessment of product change controls. As a result, end users have independently developed change control processes or risk assessments based on their knowledge of biopharmaceutical processes and understanding of known correlations of raw material variability to process/product impact. Table A summarizes the types of change controls typical of the SUS.

The suppliers' change notifications are categorized as having a high, medium or low risk impact on the processes or products. Change notifications which may be communicated from the supplier to the end user that are not directly technically related such as name change, change of CoA format, change in corporate address are considered to be out of the scope of this guidance. The overall risk associated with the change was determined through a risk assessment process where the scope includes drug substance as well as drug product containers or vessels.

Four evaluation criteria were used to assess the risk:

- **Evaluation time** – the span of time from initial notification of the change to understanding the effect, including experimental work if required.
- **Amount of testing/data required to evaluate change** – based on the quantity of data that is required to show a difference that a change may occur based on previous experience.
- **Scientific understanding of the effect of the change** – judged by the current level of data available examining the change's effect on the equipment properties.

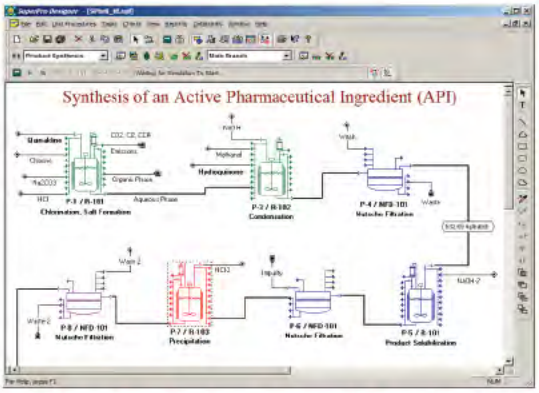
Change Control	Overall Risk	Degree of Difficulty to Implement (Risk Assessment)			
			Amount	Current	
Supplier Change Notifications		Evaluation Time	Testing Required	Science Understanding	Impact on Bioprocessing
Type 3: Change Control Notification and Full E/L and Physical Characterization					
Qualification of new polymer/resin for all components of assembly	81	3	3	3	3
Changes to current polymer/resin from all component of assembly	81	3	3	3	3
Changes to the manufacturing process (including automation)	54	3	2	3	3
Qualification of new manufacturing plant not like for like	54	3	2	3	3
New Process contact subcomponents resins	36	2	2	3	3
Raw Material Suppliers in BRIC countries	36	2	3	2	3
Type 2: Change Control Notification and Targeted E/L and Physical Characterization					
Changes to shelf life of the materials	24	2	2	2	3
Change in manufacturing location of product contact material	24	2	2	2	3
Qualification of new sub-supplier for manufacturing	16	2	2	2	2
Changes to compliance with Pharmacopoeia status (USP, EP)	16	2	2	2	2
Change in sterilization procedure	16	2	2	2	2
Change in equipment or line used in the process	16	2	2	2	2
Type 1: Change Control Notification and No Requested					
Change in the testing procedure for release and COA	8	2	1	2	2
New sterilization supplier or site (change of supplier, equipment)	8	2	1	2	2
Change in room classification or any facility related changes	8	2	1	2	2
Change in testing laboratory	4	2	1	2	1
Change in distribution route	4	1	1	2	2
Change in raw material release process	4	1	1	2	2
Quality changes EM program	4	1	1	2	2
Changes to non-process assemblies	2	1	1	1	2
Change in packaging and labeling, shipping conditions	2	2	1	1	1
Change in inspection procedure	2	1	1	1	2
Change in part number	1	1	1	1	1

Table A. Example change controls, related primarily to SUS, are categorized as having potentially high, medium or low risk of impacting the process or products.

Intelligen Suite®

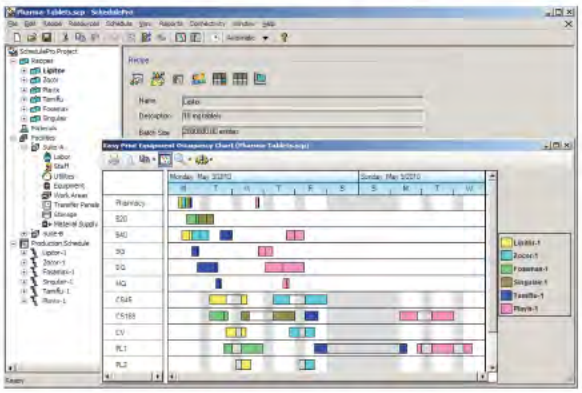
The Market-Leading Engineering Suite for Modeling, Evaluation, Scheduling, and Debottlenecking of Multi-Product Facilities

SuperPro®

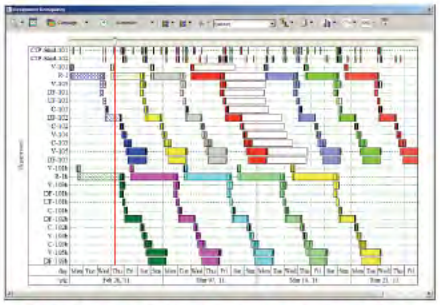


Use SuperPro Designer to model, evaluate, and optimize batch and continuous processes

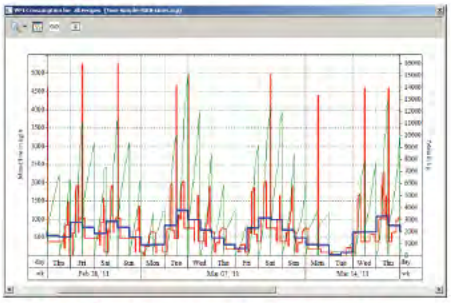
SchedulePro®



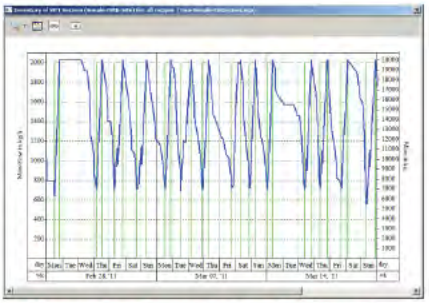
Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



Easy production tracking, conflict resolution and rescheduling



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



Managing inventories for input, intermediate, and output materials

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine 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 500 companies and 900 universities around the globe (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. 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 shared utilities, determine 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

- **Effect on bioprocessing** – the likely impact to the process, based on the typical use of the piece of equipment in the process, and subsequent impact to biopharmaceutical process.

Each of these criteria, as shown in Table B, was given a relative rating ranging from 1 (lowest risk) to 3 (highest risk). Subsequently, an overall risk score was calculated as the product of the ratings and categorized as Type 1, Type 2, and Type 3 changes, wherein Type 1 represents the lowest risk.

The change control process outlined is predominately focused on the impact of changes on the E&Ls and key physical polymer properties. Changes to the polymer identity or polymer processing that effect the form, fit or function of the final part also should be considered and addressed as part of the risk assessment. For E&Ls, start first with your company's E&L evaluation policy. If the item being changed did not need E&L testing after the original assessment, this may become a Category 1 change that doesn't need E&L re-performed.

One consideration is the documentation received with the notification of change. Some of the more common changes that may require targeted E&L testing are found in Table 1. Some questions you might ask include:

- Did the supplier or their sub-supplier perform sufficient E&L testing of the new item?
- Do you fully understand the described change and how it may affect the item?
- Where is the item used in your process (upstream or downstream)?
- Is it a location change with new equipment that works differently?
- Are they extending the shelf life of the material?
  - If so, how does it affect the E&L profile?
- Is there a change in the sterilization procedure?
- Is it a dose change, a procedural change, or a location change?
- Is there an audit procedure in place with the manufacturer of the item being changed, and the manufacturer of the assembly the item is used in?

The answer to these questions allows one to better determine the scope of the change and the potential risk of the change. Each change has the potential to affect the product in contact with the process. However, the answers to these questions may make the change a Category 1 no testing, Category 2 targeted testing, or Category 3 full testing. Ensure that you consider potential impacts of the change thoroughly.

Criteria	Rating
Evaluation Time	
0 – 2 months	1
2 – 12 months	2
> 1 year	3
Amount Testing/Data Required	
Minimal	1
Moderate	2
Significant	3
Science Understanding	
Not necessary	1
Science well understood	2
Science not well understood	3
Impact on Bioprocessing	
Low	1
Medium	2
High	3
Overall Risk Score	Range
Low	1 – 15
Medium	16 – 30
High	> 30

Table B. Risk criteria was given a relative rating from 1 to 3; a rating of 3 was of greater risk.

Type 3 Changes

Changes that have the potential to significantly impact bioprocessing or patients require extensive testing and are classified as Type 3 or major changes. These changes include:

- Qualification of a new (alternate) polymer/resin for any component of the assembly
- Changes to current polymer/resin for any component of the assembly
- Changes to the manufacturing process (including automation)
- Qualification of any new manufacturing plant which is not like-for-like for an existing plant
- New process contact sub-components and additives in the resin
- Raw material suppliers expanding into emerging countries

Major changes require extensive studies at both the supplier and end user sites to evaluate the impact on drug substance as well as drug product. These changes necessitate an end user to repeat all E&L studies, perform physical and mechanical characterization studies and (potentially) shipping studies for the impacted SUS component(s). Established understanding of the correlation between the changes and potential impact on the process or patient can streamline the testing required by the end users; however, this established understanding is not always guaranteed as it is dependent on the complexity of the process and at what stage a change is introduced.

In addition to the E/L, physical and mechanical characterization, end users also may need to repeat stability and process validation requirements in the storage vessel. Stability testing can require a one to two year evaluation period before the change can be accepted. Consequently, suppliers would need to consider these timelines to determine the time between notification and implementation of change at their or sub-suppliers' facilities.

Type 2 Changes

Category 2 changes are moderate changes that can impact bioprocessing. These changes necessitate a targeted E&L comparability study for the SUS component(s) or assembly. This can cause a delay in implementation of the item at your company which becomes an issue if notification of the change is not received with a long enough lead time. The lead time necessary would include the initial change evaluation, targeted E&L testing and results, and change control documentation required by your company.

Examples of such changes include:

- Changes to duration of shelf life of the SUS
- Change in manufacturing location of product contact material
- Qualification of a new sub-supplier for manufacturing
- Changes to compliance with Pharmacopoeia status (USP, EP, JP)
- Change in sterilization procedure
- Change in equipment or line used in the process SUS

Type 1 Changes

Type 1 changes are minor low risk changes. These changes should be communicated and verified through a standard change notification process. They should not require additional studies beyond those already completed for E&L. Examples of such changes would include:

- Like-for- like non-process contact substitutions
- Changes in qualified service providers (sterilization, assay labs, etc.)
- Changes in qualified sterilization site
- Changes in sterilization equipment providing the same sterilization method
- Changes in part number
- Changes in inspection procedure
- Changes in procedures related to packing and shipping

These changes have a low probability of affecting the product in contact with the process, as long as the quality systems are maintained and rugged.

Looking Forward/Recommendation

All evaluations were done based on a working knowledge of SUS equipment by the various authors from each of their companies. However, each process and product is slightly different. In addition, the stage of the product in development and the risk tolerance of the company may influence the adjudged risk. Thus, this risk assessment should serve as guidance, but may not reflect the experience of a particular product or process. As such, a risk assessment should be done by each company and the result should be part of an overall quality agreement with the supplier. Additionally, authors would like to recommend collaboration between end users and suppliers to agree on the change control requirements.

About the Authors

Sally Kline joined the Operations Technology Group at Amgen in 2011, where she is currently the subject matter expert for plastics in the Materials Science Group. She is responsible for raw material risk assessments, technical supply chain due diligence and understanding the impact of Single Use Systems (SUS) materials on biopharmaceutical manufacturing processes. She is an active member of the ASTM E55 Committee and BioPhorum Operations Group (BPOG) disposables work stream. Prior to joining Amgen, she had extensive experience as a Global Technical Polymer Director leading start-up ventures and Fortune 100 company team efforts in new product development, technology commercialization, technology transfer and licensing, and collaboration with universities, research institutes and government agencies.

Ekta Mahajan is a Senior Engineer in Pharmaceutical Technical Development Engineering group at Genentech/Roche in South San Francisco, CA. In her 10 years of research and manufacturing experience in biotechnology, vaccines and pharmaceuticals, she has lead projects in a wide range of areas, both upstream and downstream, including commercial manufac-

turing support, process development, and new technology evaluations. Mahajan has expertise in disposable technology and is currently leading projects for design and implementation of disposables in development and manufacturing including drug conjugates. She is an active member of BioPhorum Operations Disposables Group, ASTM Working Group and co-chairs ISPE single use community of practice. Before Genentech, she worked as a Staff/Senior Engineer in the Technical Operations and Engineering and the Technology Departments at Merck. Mahajan has a BS in chemical engineering from the Thapar Institute of Engineering and Technology (TIET) in Punjab, India and a MS in chemical engineering from Bucknell University.

Darrell Morrow is Director of Quality Assurance at Acceleron Pharma, a company developing medicines that regulate the transforming growth factor beta (TGF-β) superfamily of proteins, which play fundamental roles in the growth and repair of cells and tissues such as red blood cells, bone, and blood vessels. Acceleron's Cambridge, MA facility utilizes single-use technology to produce bulk drug substance for the manufacture of a robust pipeline of protein therapeutics targeted to key mechanisms underlying blood diseases and cancer. Morrow holds a BS from the New York State School of Industrial and Labor Relations at Cornell University. He has 18 years of quality assurance experience at all stages of drug development from research through commercial in various roles at Sanofi Pasteur, Acambis, and Genzyme Tissue Repair (Biosurgery). Morrow is a certified Project Management Professional and is a member of ASQ and PMI.

Bob Steininger joined Acceleron in March 2007 as Senior Vice President, Manufacturing. He is now responsible for managing the process development, analytical development, manufacturing, and validation personnel that are involved in making clinical trial material in Acceleron's single-use-equipment-based manufacturing facility. He was previously the Vice President of Process Sciences at Millennium Pharmaceuticals. In this capacity, he was responsible for development of the bulk production processes for both large and small molecule clinical candidates and managed the development group which made Millennium's first internally developed biologic using single use bioreactors. Steininger also served as a VP within the Millennium Product and Portfolio Management organization. Prior to joining Millennium, he held multiple roles at Genetics Institute (now Pfizer Pharmaceuticals) from 1984 to 2000, including Director of Clinical Production, Director of Process Technology, Director of Regulatory Affairs, and Senior Director of Research, Genomics. He is currently a director of the Massachusetts Accelerator for Biomanufacturing Corporation and Sunopro Corporation. Steininger is a founding member of the Mass Biomanufacturing Roundtable of the Mass Biotech Council, Chairman of the ASTM Subcommittee on Biotechnology Standards, a member of the advisory board of Chemical Engineering Department of the University of Massachusetts, Amherst, the Bunker Hill Community College, and of the RISTA program of the Cambridge Rindge and Latin High School. Steininger received a SB in chemistry from Massachusetts Institute of Technology and an MS in chemical engineering from the University of California, Berkeley.

Nancy Sweeney is a Senior Scientist in the Manufacturing Technical Support group at Gallus Biopharmaceuticals in Saint Louis, Missouri. Prior to joining Gallus, she was a scientist at Janssen, Wyeth, Restoragen and Pfizer bringing 19 years of biopharmaceutical experience in both cell culture and purification research, clinical, and commercial production. She has expertise in tech transfer and process scale up, bringing development drugs to commercial production and is currently leading the leachable and extractable program at Gallus. This includes implementation of their new disposables production suite utilizing FlexFactoryTM biomanufacturing platform and other disposable systems. She has a BS in molecular biology and chemistry from the University of Nebraska at Lincoln. She can be contacted by email: nancy.sweeney@gallusbiopharma.com.

Gallus Biopharmaceuticals LLC, 4766 LaGuardia Dr., St. Louis, Missouri 63134, USA.

Russell Wong is currently Senior Manager, Manufacturing Sciences Raw Materials at Bayer Healthcare in Berkeley, California. He specializes in the implementation of single use systems trouble shooting, assembly design for reliability, and new technology evaluation. Dr. Wong received his BE in chemical engineering from the Cooper Union and an MS from the University of Utah in bioengineering. He completed his PhD at the University of Tennessee in polymer engineering with research into biomedical polyurethanes used for cardiovascular implants. He began his career with Monsanto Plastics (later acquired by Bayer) in Springfield, Massachusetts where he developed specialty plastic formulations for engineered applications. Dr. Wong is a member of the PDA Single Use Task Force and the BioPhorum Operations Group Single Use Systems Teams.

Seeking practical GMP solutions to meet regulatory requirements?

Take ISPE elearning

NEW EXPANDED COURSES:

THE DEPTH OF AN IN-PERSON CLASS, ONLINE.

ISPE | GAMP® — ISPE, the Developers of GAMP®

- GMP Auditing for the Pharmaceutical Industry
- Biotechnology Basics
- Containment Fundamentals
- Basic Principles of Computerized Systems Compliance: Applying the GAMP® 5 Guide: A Risk-based Approach to Compliant GxP Computerized Systems

Acquire the knowledge you need immediately with over 150 offerings in 22 topics. Try a free demo at www.ISPE.org/FreeModule.

REGISTER TODAY!
www.ISPE.org/eLearning

ISPE

Invest in the future and get free registrations for sponsoring an online training course. Contact apachella@ISPE.org for details.

How Does Strategic Planning Help to Mitigate Risks in the Pharmaceutical Supply Chain

by Agnes Trouchaud

This article presents the implementation of a key strategic planning process to mitigate risks in GSK's API supply chain; it was adapted from an ISPE France presentation held in June 2013.

Because of the quick evolution of its portfolio, including a significant number of new product launches, molecules going off-patent, and increasing financial constraints, GSK has to manage a more complex supply chain making it even more critical to optimally manage its primary API supply.

In an effort to better manage risk, GSK has implemented a key strategic planning process to help identify the risks associated with the product lifecycle, their market, and the global supply chain, enabling them to successfully study and launch projects.

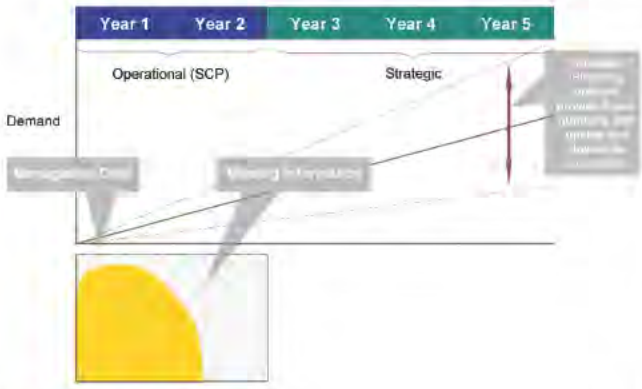


Figure 1. API planning levels.

With the implementation of robust planning processes, GSK is able to work toward its goal to have continuous control over the proper size of the network – an important part of its program of excellence.

To put it in context, GSK has 37 secondary sites which produce a large variety of drugs, including oncology, respiratory, infectious diseases, HIV, neurosciences, cardiovascular, metabolic, etc. It has eight internal sites and approximately 200 external sub-contractors that supply more than 300 APIs. Among those, 80 are managed by the Primary Business Planning (PBP) team responsible for either revenue or medically critical drug products, including New Chemical Entities (NCE).

Main Characteristics of the Primary Supply Chain

GSK follows a "Make to Forecast" model based on commercial forecasts to determine when to manufacture primary (API); while the decision to move forward with secondary manufacturing is based on a "Make to Order" model. The focus of this article is on GSK's strategy for mitigating risks in its primary pharmaceuticals supply chain; secondary manufacturing is not discussed.

The "Make to Forecast" model is mainly driven by the long manufacturing lead times for APIs (some are more than 12 months) due to:

- Multi-stage processes with a multiplication of the number of chemical steps to obtain an API

ELETTRACQUA

pure water technologies

SINCE 1966

PHARMACEUTICAL WATER SYSTEMS

OSMOSIS + EDI UNIT HOT WATER SANITIZABLE

DOUBLE PASS REVERSE OSMOSIS | 4m³/h - 32 GPM
HIGH TEMPERATURE SANITIZATION + CONCENTRATE RECOVERY SYSTEM

MULTIPLE EFFECTS DISTILLATION UNIT

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

Figure 2. Key supply chain processes.

- Campaign effect of batch processing
- Capacity limitation due to interaction of processes on multi-purpose plant
- Labor restricted use of plant
- Long lead time to implement extra capacity

The "Make to Forecast" model is also driven by raw materials, intermediates, and API's procurement constraints with:

- Long procuring raw material processes (some up to nine months)
- Growing expenditures and use of external suppliers requiring longer lead times
- Contractual obligations with the suppliers (some requiring firm order 3 years in advance) with few "Take or Buy" contracts in place
- "Turn on and off" impossible at short notice without losing credibility and flexibility with the suppliers

Today, API facilities are manufacturing what was decided two to three years ago. As a result, under forecasting can lead to supply constraints, which may take years to recover from, making it even more critical to have robust planning processes in place to understand and anticipate forecasts variability.

Two levels of API planning: operational/tactical and strategic – each one having its own process and data are depicted in Figure 1.

The purpose of operational/tactical planning is to manage firm sensitivities and operational changes within a 2 year timeframe. This is done through a site based monthly process (Supply Chain Planning process) and is made up of a number of sub process steps: demand review, capacity review and consolidation and scenario planning. Purpose of this SCP process to first ensure that supply meet demand with maintaining the appropriate stock level but also to highlight any demand sensitivities and derived capacity constraints through scenario planning. A monthly Above Site SCP review is then held, purpose of which is to endorse production/supply plans and to make decisions on option/recommendation to mitigate notably risk of supply interruptions.

Strategic planning focuses on year 3 + timeframe. Strategic planning consists of two main sub processes: long term demand review (carried out through Product Review Forum process) and long term capacity review that followed the demand review. Strategic planning leads to more strategic decisions, such as investment on site, introduction of new API sources.

Risks on the Primary Supply Chain

GSK used a set of standard Ishikawa diagrams to define the type of risks that could possibly impact its supply chain. In parallel to using Ishikawa diagrams, GSK performed a SWOT analysis (strength/weakness – opportunity/threat) as well conducted audits, specific studies, and operational measurements. Figure 2 presents the model used by GSK's Global Manufacturing System.

More details are provided in the Ishikawa (fishbone) diagrams located at www.pharmaceuticalengineering.org.

Planning and Risk Management Processes and Tools

There are Two Key Principles to Supply Risk Management

- Consider risk to supply situations (catastrophic loss, step

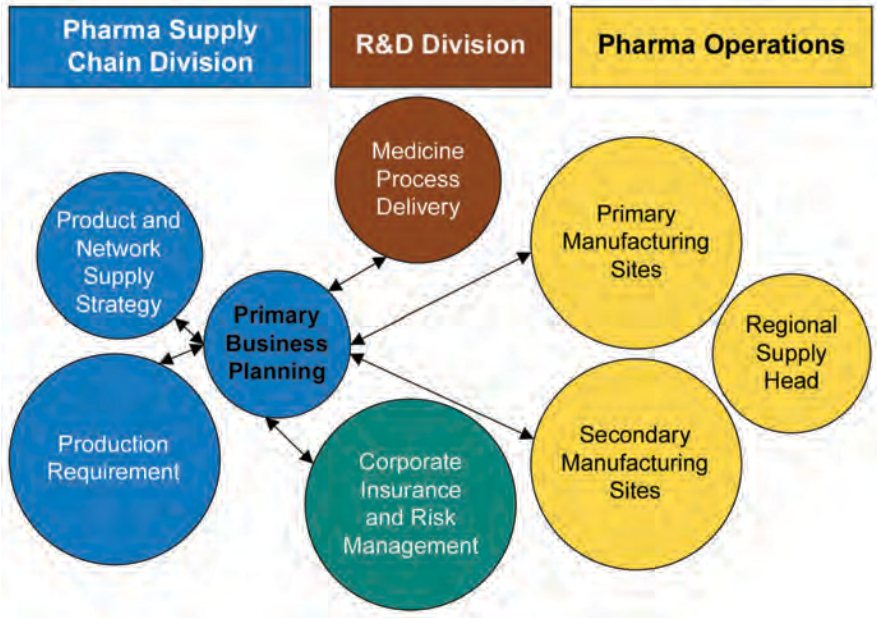


Figure 3. The key roles of PBP and its relationships in the whole structure.

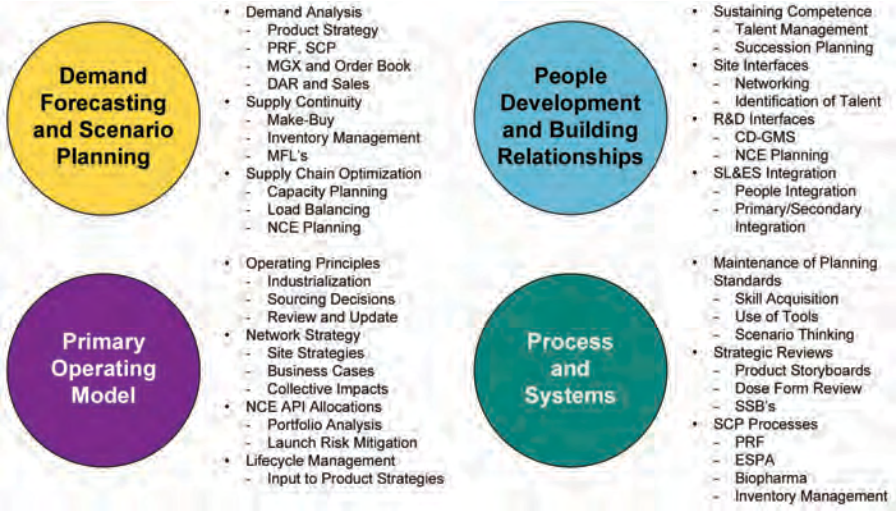


Figure 4. The four main competencies of PBP.

increase in demand, etc.)

- Organize workshops involving the sites, the Primary Business Planning (PBP) team, and the Procurement and Strategy teams to review the risks for the critical internal sites and third parties; review and agree on what to do to mitigate the risks - *Figure 3 and Figure 4.*

Product Review Forum (PRF), the Strategic Planning Process

The Product Review Forum (PRF) is at the cornerstone of API demand forecasting and scenario planning. This annual process consists of a 5 years demand review and of the supply plan to meet this demand. The key competence for this process is the ability to understand the long term business requirements to ensure what we make/buy today will maintain appropriate inventory levels. The purpose of the demand review is to agree the best view of the demand but also to understand all possible demand scenarios.

The PRF must review and identify drivers of upside and downside demand, what will be impacted as a result, particularly the external supply chain, develop responses to all scenarios with timeframe and costs, consider any technical difficulties and resolution time, and finally understand when to implement a response. The commercial group will conduct this review once a year or more often depending on the urgency.

The PRF is an event that is organized once a year. It supports the Supply Chain Planning (SCP) demand review process (0 to 2 years), but does not replace it. The PRF identifies what drives the sensitivities that then need to be tracked through the SCP process - *Figure 5.*

The PRF provides a five year demand which allows capacity utilization to be forecasted for commercialized products using standard templates and definitions. A forecast for new products based on a standard model (developed by R&D) of likely launch success and upside launch success is overlaid on the commercialized products. Site and network capacity utilization graphs are then developed for capacity of various types of internal and external manufacturing resources – large, medium, small or special. Scenario planning will allow decisions to be made in the long term around sourcing strategies and tactical use of plant for the retention of capability.

It is important to ensure that tactical use of a plant will align with the long term strategy for the site and the external supply chain. It is too easy to be focused on short-term operational benefits without understanding what this will mean in the long term – particularly the loss of flexibility and potential increased costs.

It is common in many companies to analyze risks continuously by updating the risk management process map and the resulting score matrix (probability of occurrence multiplied by impact). An exception to this scenario is when there is no way to mitigate the risk, which leads to a plan aimed at eliminating the root cause of the risks, minimizing their impact, decreasing their probability of occurrence, or transferring or sharing the risks.

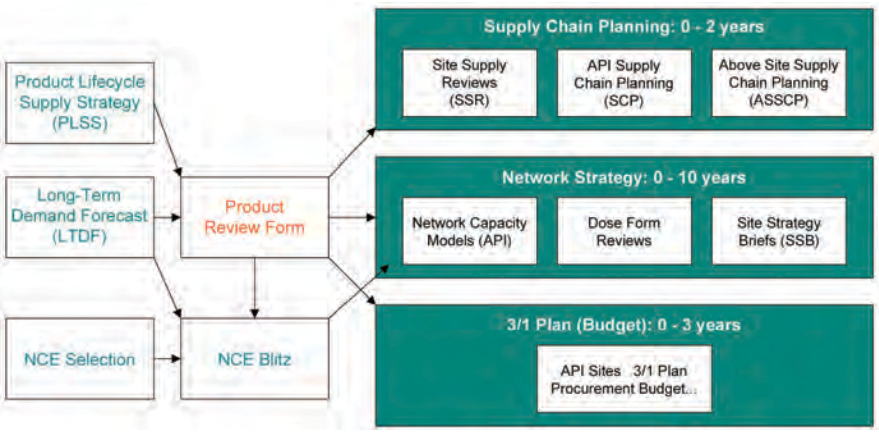


Figure 5. Key strategic and tactical planning processes.

Focus on Outsourcing

Shortages in the supply chain may actually occur at suppliers and subcontractors sites; therefore, the same risk management rules must be applied

to external sites. Those risks must be mitigated by implementing a robust Business Continuity Plan and processes to ensure that those sites do not add additional risk to the supply chain. Three key axes are taken into considering: security of supply, quality/regulatory, and performance as seen in Table A.

Security of Supply
• Understand the Supply Market Size, Importance of pharma supply as well as GSK in the market
• Stockholding/Safety Stock (quantity/time/money) *Raw intermediates plus final product to GSK safety stock at GSK and Suppliers. Is it all located in one place or multiple? Last time checked/covered by contract?*
• Sole supplier/multi-sourced?
• Capacity constraints *Industry as a whole and individual suppliers*
• Lead-times
• BCP Supplier Disaster Recover plans in place?
• EHS Audit Status
• Logicstics and distribution plans/methodologies
• Geography *Lead times implication, areas of natural risk*
Regulatory
• Annual Updates
• Registered Supplier/Site/Commodity
• Time taken to approve alternative suppliers/site of manufacture
• Number of regulatory events that GSK will have to manage as a result of change
• Supplier willingness to be audited by regulatory bodies
• Supplier performance in regulatory audits, e.g., FDA
• Stability testing required to change supplier
Quality
• Last audit status? (full approved/conditionally approved/not approved)
• Critical findings?
Performance History
• Customer feedback
• Relationship management – proactive/reactive

Table A. Three axes: security of supply, quality/regulatory and performance.

GSK has implemented a process to help evaluate the threat every supplier potentially poses to the product supply chain by completing an internal questionnaire dedicated to risk scoring and by submitting it to an internal expert. This API supplier questionnaire may be developed using elements from a standard survey and a Q7-GxP survey.

It is important to ensure that tactical use of a plant will align with the long term strategy for the site and the external supply chain.”

Depending on the result, this may trigger a Loss Prevention Audit by the Insurance and Risk Management (IRM) Department, which could result in the Supply Chain Manager, the Procurement Manager, and IRM generating an action plan. This action plan or realistic risk improvement strategy should be implemented over an agreed timeframe with the supplier. If an audit is not triggered, the Supply Chain Managers involved must make sure that Business Continuity Plans issued by Corporate Insurance and Risk Management group are in place at an appropriate level.

Conclusion

There are three main benefits of developing a process for API strategic planning:

- A better alignment between the long term business strategy and the order management process
- A better consistency between the plans built to meet the markets requirements at the best cost
- An implementation of protection measures and risk management rules which secure continuously the appropriate stock levels

About the Author

Agnes Trouchaud is a Senior Analyst working at the Supply Chain Strategic Division of GSK Pharmaceuticals in London. She had worked for more than six years at the API Strategic and Tactical Planning department of GSK Pharmaceuticals. After completing her studies at Rennes Business School and Ecole des Mines de Paris, she worked successively for Leo Animal Health and Ipsen Laboratories on Supply Chain projects. She can be contacted by email: agnes.x.trouchard@gsk.com.

2014 ISPE ANNUAL MEETING

12–15 October 2014

Caesars Palace ▸ Las Vegas, Nevada USA

Exchanging Ideas
Advancing Technology
Expanding Networks

Investigational Products
Information Systems
Manufacturing Facilities and Design
Manufacturing Technology
Project Management
Quality Systems
Regulatory and Compliance
Technical Showcases
Young Professionals

www.ISPE.org/2014AnnualMeeting

Transfer Station Design for Large Scale API Manufacture (Part One)

by Joseph R. Hettenbach, P.E.

This article presents Part One of a two part article describing the background bases and philosophies applied to the development of detailed layout of process manifold rooms and of the process service rooms.

Background and Overview

Process transfer stations, also referred to as *process manifolds*, have been an integral part of multi-product API manufacturing plants for decades. This subject matter will be presented in two parts. Part One describes the background bases and philosophies applied to the development of detailed layout of process manifold rooms and of the process service rooms.

Figure 1 offered as an introduction to this subject matter, is a 3-D computer generated picture of a typical *process transfer station*. This *"picture"* is a partial section extracted from the 3-D design model for a major multi-product API facility produced during the detailed design phase for the project executed, in the early 2000s. The design model was utilized as a ready reference tool during the construction phase of that particular project, and this "picture" depicts a section of that *process transfer station* that was actually built consistent with the detailed information derived from that design model (in addition to "isometric drawings" of all of the pipe lines).

In the mid to late 1980s, these systems were further developed with regard to their design, integrating improved operability, greater flexibility, and compatibility with emerging more stringent Environmental Health and Safety (EH&S) and Quality Operations (QO) regulatory requirements. The design features for these systems will vary depending on the application, i.e., a new facility versus an upgrade or expansion of an existing plant with the physical constraints and considerations peculiar to the application governing the installation; constructability issues and capital cost also are

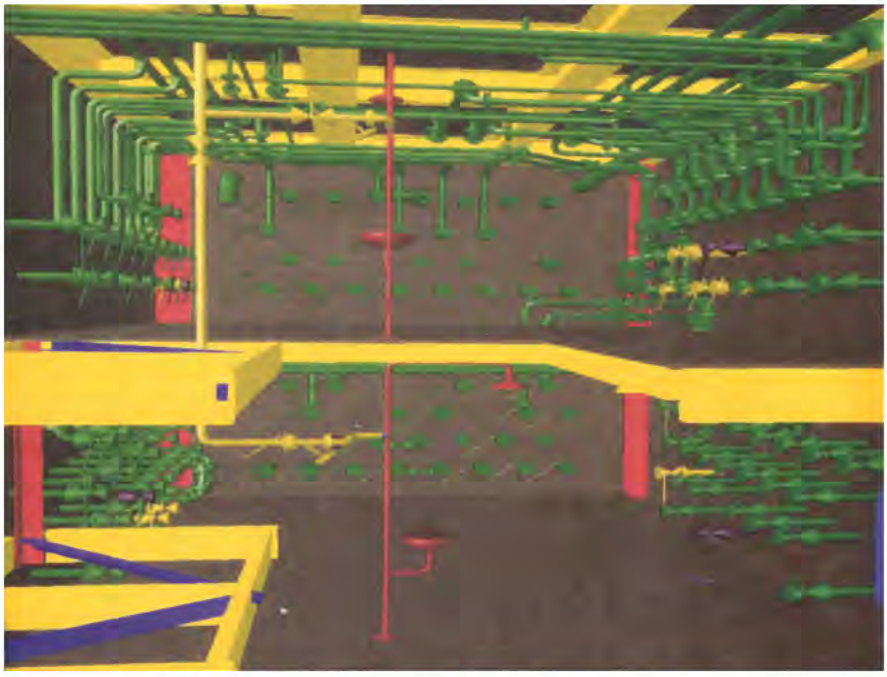


Figure 1 .Computer generated 3-D depiction of an actual process transfer station.

Finesse.com

Eat or be eaten.

Contaminants shouldn't have a chance.

Keep your media from being someone else's lunch. Our single-use sensors protect your bioprocess from predatory micro-organisms that can overrun cells and ruin your batch.

Finesse single-use sensors: SmartPuck pH+dO$_2$, TruFluor pH, TruFluor DO, and TruTorr block external contaminants. The sensors are inserted or welded into the bioreactor bag before sterilization. The readers never contact the media so the sterile barrier remains unbroken. TruFluor pH and TruFluor DO also have temperature-sensing capability, so no additional temperature sensor is needed.

All of the wetted materials are USP class VI and ACDF certified. Sensors are pre-calibrated, provide industry leading precision, and are plug-and-play in most any system.

Don't let other people's sensor claims leave a bad taste in your mouth.

Finesse Single-Use Sensors

SmartParts > SmartSystems > SmartFactories > Smart Bioprocess Solutions > Finesse.com

important considerations.

The basic detailed design of these systems has evolved with greater attention being afforded to details such as the type and specification of the "flexible connectors" (the FDA preferred name for "hoses") that are connected in the transfer stations to nozzles on the walls. These nozzles are connected to piping outside of the walls, including use of automated valves to allow flow "to" and "from" the process equipment and the completion of *piping circuits* between the pieces of equipment. The size, length, the Materials of Construction (MOC) of the hoses and the types of "ends" (e.g., flanges, quick-connect couplers, etc.) which are provided to effect the connections to the nozzles located on the "face" of the manifold walls also are important. The manifold system consists of a number of pipe spools with nozzles coming through a wall into the transfer station, having the appropriate matching "ends" (connection type) for the hoses. These spools are either supported in an open secured structure or integral with a metal plate with chemically resistant tile facing, as needed.

The manifold system can be located out on the process floor or in some enclosure – a booth or a room. Both *contemporary standard* (transfer stations in rooms) and alternative *acceptable standard* type design approaches will be described in this article. Transfer stations are not necessarily enclosed in a room. In addition to the use of hoses making "connections" on a wall face, it is also useful to utilize removable interchangeable pipe spools in piping systems within the transfer station rooms and beyond the boundary limits of those rooms. Out on the process floor, removable spools and *swing* pipes can be used, as well as at inlet nozzles on the top of reactors (and other equipment), and in the outlet piping systems of that equipment. These features allow the flexibility of changing the piping to accommodate the needs of a specific process.

While the primary process transfer stations (e.g., as illustrated in Figure 1) provide the means to interconnect process equipment, a number of other transfer stations and rooms can be set up to better manage: mother liquor and waste stream activities, process vacuum services, and charging of gases and liquids from containers to the process equipment. All of these rooms have the means to make the necessary connections, via the use of hoses on nozzles to pipe lines which terminate in the main process transfer stations, and also have lines going to other destination points (e.g., mother liquor tanks) to cover the process needs.

Transfer Stations and Special Service Rooms

- Main (primary) process transfer station(s)
- Process vacuum transfer station(s)
- Head tank charging transfer station(s)

These will be described in more detail in the "Index Tables for Transfer Stations" below.

Contemporary Standard Approach for Process Transfer Stations

For new facilities, and for revamps/expansions of existing

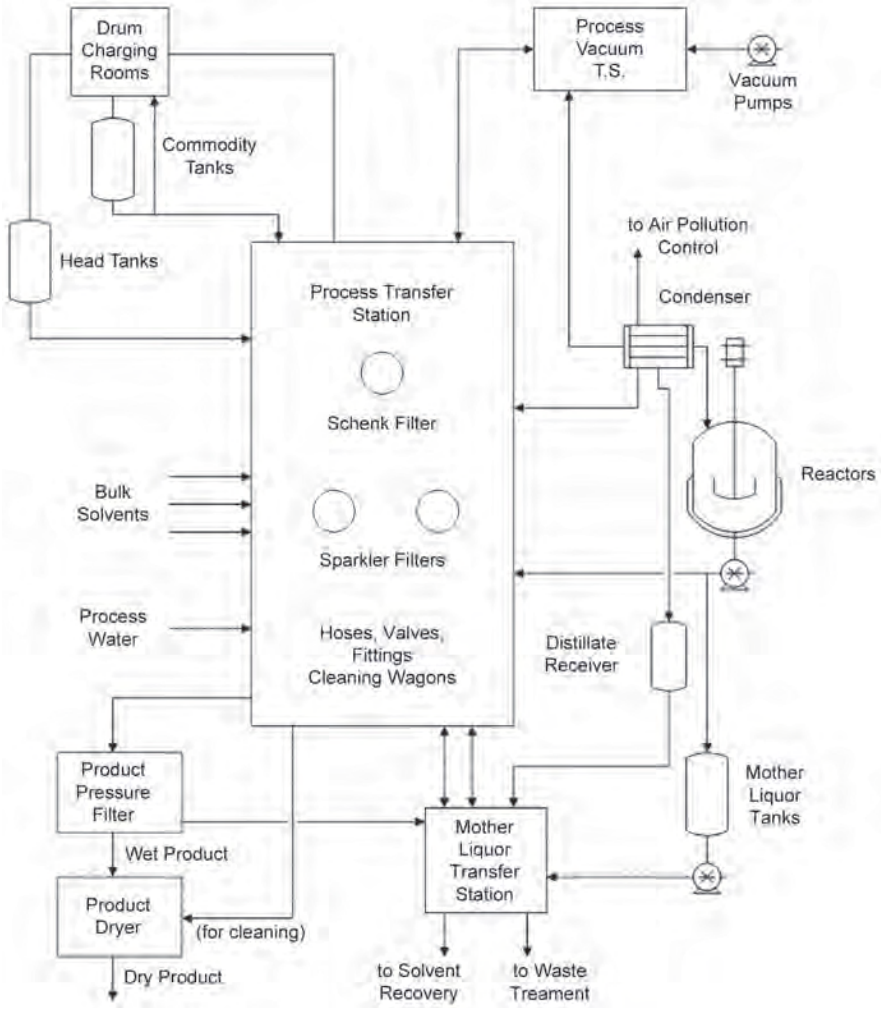


Figure 2. Example of a process manifold system network schematic.

facilities where there is enough space available for a transfer station room and associated required piping, etc., it is desirable to have a room for the transfer station, located in the building where explosion relief panels can be utilized on at least one wall. The first step in the development of a process manifold (system) for a multi-product facility is to create detailed Index Tables (described and illustrated below, in the *"Index Tables for Transfer Stations"* section. These Index Tables A, B, and C list all of the "connections points," i.e., effectively allowing for the *completion* of process lines, using hoses in the separate manifold rooms/areas in a *flexible piping* network (as opposed to totally hard-piped process systems); as well as the "interconnectivity" required between theses rooms. The numbers and types (services) of "connecting points" in the rooms are determined by process engineers, referring to equipment P&IDs and a number of process flow diagrams which together describe the "completed" process piping that must be achieved to satisfy all of the process flow needs. In addition, process cleaning and miscellaneous services, such as managing waste streams, etc., must be accommodated. Previous experience from successful operating plants is also a key in determining the counts for the "connection point types," e.g., the number of feed lines to a reactor and the number of outlet lines required, etc., for a number of potential processes to be run in the facility.

Figure 2 is a schematic depiction of a single reactor with all of its major support equipment and other process equipment used in running a process with process lines routed to the main process station and the other type transfer stations. In addition typical "connections" between the process transfer station and the other transfer stations/rooms that effectively complete the *circuits* of the process piping required, including the support services, are shown – as just one example of a typical *"system network."*

Index Tables for Transfer Stations

Examples of process manifold index tables are illustrated, below. The basic data for these tables was extracted from an actual complete index table which was developed for the front end design study of a proposed fill-out/expansion of an existing large API building located outside of the U.S., using general equipment names (not the specific equipment numbers that were specified in the actual index tables for that project).

It should be noted, for the record, that management had decided not to go forward with that particular project, due to changing market conditions. The complete index included the lists of equipment and associated services to be installed/accommodated in the facility. The numbers of the "connection points" for different type of services comes from some operating experience as well as the study of a number of different processes that potentially can be run in the facility, each with its peculiar equipment set and specific process

flow needs. Examples of these would be connections for feed lines to reactors and other equipment; outlet lines from reactors and other equipment; and connecting points to allow charging of liquids to reactors and other equipment, and discharging of waste liquid streams for subsequent treatment, solvent recovery etc. In addition, the main (primary) process transfer station would ideally have two levels (shown in this example index table as an upper mezzanine level, and a lower, floor level).

Data Basis for Index Table Contents

For the purposes of illustrating the concepts involved in the development of the process manifold index tables, the following abbreviated major equipment list was used, representing on a smaller scale (in terms of equipment piece numbers) the multi-product API plant we were designing:

- Two reactors with pumps, and overhead condensers
- One distillate receiver
- Two head tanks (general purpose liquid chemicals)
- One commodity tank (for specific chemicals such as sodium hydroxide (48 w/o)) hydrochloric acid (37 w/o), and sulfuric acid (98 w/o)
- One filter (e.g., for a carbon filtration)
- Two sparkler filters (for removal of lower levels of undesired solids from a solution)

SERVICES	WALL	INL	LEV	INL	LEV	DIST LINE	LEV	OUT	LEV	LINE TO PVTS
Reactor 1	S	3	M	2	L	1	L	3	L	1
Reactor 2	N	3	M	2	L	1	L	3	L	1
Distillate Receiver 1	N					1	M			
Head Tank 1	N	3	M				L	1		
Head Tank 1	N		M	1						
Head Tank 1	N						L	2		
Head Tank 2	N	3	M				L	1		
Head Tank 2	N		M	1						
Head Tank 2	N						L	2		
Schenk Filter	N	1	L				L	1		
Sparkler Filter 1	N	2	L				L	2		
Product Pressure Filter 1	S	2	M				L	2		
Receiver Product Pressure Filter 1	S			1	M					
Product Pressure Filter 1 APOVAC	S			1	M		L	1		
Product Dryer 1	S						L	1		
Product Dryer 1 Vacuum Pump	S						L	1		
Filter Dryer 1	N	2	M				L	2		
Filter Dryer 1 COMPOVAC	N			1	M		L	1		
Mother Liquor Tank 1	S	2	L				L	1		
Mother Liquor Tank 2	N	3	L				L	1		
	WALL	INL	LEV	OUT	NOTES					
Commodity Tank 1	S	1	M	1	Overhead Splits to N&S					
Process Vacuum Pump 1	S	1	M							
SERVICES	CONN.	W	LEV		NOTES					
Runner to and from Drum Charge. Rm.	1	N	M							
Runner to and from Drum Charge. Rm.	1	S	M							
Runner to and from Drum Charge. Rm.	1	N	M							
Solvent Line #1 (of 8 in total)	4	2 splits overhead to N and S walls at M level								
SERVICES	CONN.	LEV								
Internal runner from N/W to SW 1	2	Below Mezzanine Platform								
Internal runner from NW to SW 4	2	On Mezzanine Below 4th floor								
Nitrogen	2 N wall, 2 S wall Overhead on M level									
Nitrogen	2 N wall, 2 S wall Overhead on L level									
Runner from E to W Wall 1 (of many)	N	2	L	Runner Outside wall from E to W						
Vertical Runner 1 (of many on N & S)	N	2	Runner from M level to Floor Level							
	WALL	CON.	LEV							
Future Runner Fr PTS-N to PTS-S	N	1	L	Runner from PTS-N to PTS-S						
Future Runner Fr PTS-N to PTS-S	S	1	M	Runner from PTS-N to PTS-S						
Runner to Mother Liquor T.S, #1	N	1	L	Runner from MLTS-N						
Runner to Process Vacuum T.S., #1	S	3	M	Runner to PVTS-N						
Routing to Strong WWTP (on N and S)	S	2	M	3	L					
Notes: 1. Some transfer stations may have 3 active walls with the fourth wall being a pressure relief designed wall (allowing for blowout, via relief panels).										

Table A. An example of a main process transfer station.

SERVICES	CONN
Runner to Process Transfer Station N #1	1
Runner to Process Transfer Station N #2	1
From Reactor 1	1
From Reactor 2	1
From Mother Liquor Tank 1	1
From Mother Liquor Tank 2	1
From Distillate Receiver 1	1
To Process Vacuum Pump 1	2
Note: One of the main functions of this transfer station is to allow the sharing of process vacuum pumps (i.e., one process assigned per pump, at a time).	

Table B. An example of a process vacuum transfer station (room).

- One pressure filter (to recover solid product)
- One filter dryer (to combined pressure filtration and drying, in-situ)
- One other type of dryer (e.g., a pan dryer or a cone dryer)
- Two mother liquor tanks (with agitation, heating and cooling, for waste treatment, etc., as well as collecting distillates, extraction layers, and mother liquors)

SERVICES	CONN.	NOTES
DTS#2>#3 Run 1	1	Connect
DTS#2>#3 Run 2	1	With
DTS#2>#3 Run 3	1	DTS#2
DTS#3>PTS-N Run1	1	Connect
DTS#3>PTS-N Run2	1	With
DTS#3>PTS-N Run3	1	PTS-N
DTS#3>PTS-N Run4	1	
	To TK	From TK
Head Tank 1	1	1
Head Tank 2	1	1
Commodity Tank 1	1	1
Notes: 1. These rooms are similar in design and function to "drum and gas handling transfer room(s)," and " drum charging transfer stations (rooms)," as well. 2. "TK" designates a tank (vessel) which is charged with liquids and used to feed the respective chemicals to reactors and other equipment. 3. Note that there were three Drum Transfer Stations in the design scope of this particular facility, from which the extracted data was obtained.		

Table C. An Example of a head tank charging transfer station.

- Miscellaneous support equipment including vacuum pumps, and auxiliary systems for the filters and dryers

Process Manifold Index Tables

Tables A, B, C are extractions of a sampling of a much larger data base for the actual planned major API facility (using generic equipment piece names, rather than actual I.D. numbers for simplicity purposes), just to illustrate how these tables are constructed, and to show the data they may include.

Background

There are usually one or more (primary) process transfer stations in number. Table A follows this text. These rooms are used to manage the reactor operations – lines to and from these rooms to run the basic processing within these vessels; and transfers between them, and to and from other auxiliary equipment and process support systems. Management of distillates from overhead condensers is included, and an overhead distribution system including a number of solvents is typically provided – 8 to 12 different solvents would not be unusual. Direct feeds are provided to reactors from liquid and gas charge rooms, mother liquor tanks and head tanks; disposition is accommodated for the transfer

of liquid waste streams to storage tanks outside of the API building to feed solvent recovery, effluent treatment and outside waste disposal operations.

It is desirable in some larger plants to have two (or more) main process transfer stations to reduce the distance between the transfer stations and the numbers of equipment pieces served. This also has the advantage of reducing the potential *clutter* effects in the room, particularly during the process cleaning operations. An equitable number of "runners" (piping with the appropriate nozzle ends) would be provided to allow the "interconnectivity" of the equipment *serviced* in the number of different transfer stations provided.

Larger facilities might have, in addition to a number of main (primary) process transfer stations, other support transfer stations for drum charging, process vacuum and mother liquor support services.

Two main process transfer stations and auxiliary support/service transfer stations rooms designated "north" and "south" were provided for this large example API plant due to the size of the building, number of major equipment pieces, and piping particulars involved.

Nomenclature Notes:

LEV = the level at which the connection is located
L = the lower level M= mezzanine (upper) level
INL = the connections for equipment inlet services
OUT = the connections for equipment outlet services
DIST = the connections for routing solvent distillates
PVTS = the connections associated with the process vacuum transfer station operations
Conn = the number of connecting points (e.g., flanges on pipe spools coming through the wall).
The wall designations are: N= the north wall, S = the south wall

An Example of a Process Vacuum Transfer Station (Room)

There are usually one or more in number of these type. These rooms are more typically located out on the process floor (or in an appropriately "electrically – hazard class rated" service area within the general open process area). These manifold stations are used to manage the flexible use of process vacuum pumps. The vacuum pumps are utilized for vacuum distillation operations and general process vacuum use. There are generally more reactors and equipment pieces than the number of vacuum pumps to service the reactors. The appropriate piping also would be provided between the reactors and selected distillate receivers and mother liquor tanks, using hoses to and from nozzles in the main process transfer station to effect the completed process lines required to balance the pressures for atmospheric and vacuum distillation operations, respectively - *Table B.*

An Example of a Head Tank Charging Transfer Station

There are usually more than one of these type rooms in number. These rooms are used for the charging of liquids from drums and containers to reactors, head tanks and wash tanks (e.g., solvents). In addition, commodity chemicals from other dedicated head tanks using concentrated commercial grades of chemicals (such as sulfuric acid, caustic soda, hydrochloric acid, acetic acid, phosphoric acid, etc.), can be routed to general purpose head tanks. General purpose head tanks also can be used to make dilute water or solvent solutions or chemical solutions for ultimate feed to reactors and wash tanks - *Table C.*

Drum and Gas Handling Transfer Room(s), also referred to as "drum charging rooms" – one or more in number- are rooms used to handle the direct addition of liquids (using portable pumps), and gases (e.g., anhydrous hydrochloric acid, ammonia, etc., from pressurized cylinders) from larger containers and cylinders to reactors, head tanks, and wash tanks.

Conclusion

Process manifold rooms or transfer stations are important components of large, flexible multi-product API facilities. The design of these type facilities requires careful planning, and attention to detail to satisfy processing, operational and product quality requirements. At the same time, safety, environmental, health, and maintenance needs must be accommodated, while following the CGMP guidance as it applies.

About the Author

Joseph R. Hettenbach has more than 35 years of process engineering and environmental engineering experience, spending 33 years at Pfizer Inc, servicing manufacturing and research facilities in many U.S. locations, Puerto Rico, Ireland, England and Singapore. He has managed the detailed process design of a number of projects for laboratory development, kilo plant, pilot plant and commercial scale manufacturing API facilities. He has made presentations on the subject of "improving the process design of multi- product API facilities" to a number of E&C, A&E and CM companies throughout the U.S., in Singapore, and in Ireland; to ISPE and to the AICHE. He has Masters Degrees in chemical engineering and environmental engineering from Manhattan College. He is a licensed Professional Engineer in New York State. He also has taught as an adjunct professor in the Graduate Environmental Technology Program at the New York Institute of Technology. He can be contacted by email: tjchett@optonline.net.

Defining Holistic Asset Criticality to Manage Risk

by David J. Mierau, PE, CMRP

This article presents how risks to safety, quality and productivity can be managed through asset control strategies, which are created based on specific asset criticality and failure modes.

The pharmaceutical and biotech industries have a wealth of information published related to risk-based practices for validation, qualification and commissioning of processes and equipment. However, these approaches typically focus exclusively on the impact of an asset to product or raw material SISPQ Strength, Identity, Safety, Purity, and Quality (SISPQ). While this is an appropriate focus area for making medicines and vaccines, there is significant business value in understanding the holistic potential impact an asset carries.

Successful pharmaceutical and biotech operations share the same foundation as other manufacturing operations: safety, quality and productivity. People within an organization use established processes (e.g., procedures, standards, programs, etc.) to achieve a stable asset performance level. As an example: manufacturing production planners use their current sales and operations plan to create a base schedule for operations so that customer orders can be met and desired inventory levels are maintained. Having some balance across all three areas of safety, quality and productivity is necessary – take away one of these aspects and the operation will not be successful. Pharmaceutical and biotech operations typically have robust quality and Process Safety Management (PSM) systems, but have not developed equally valuable productivity systems.

Understanding and quantifying how each of these areas specifically impacts the overall operation is the genesis of developing a Risk-based Asset Management[SM] program, which maximizes productivity while maintaining focus on safety and quality. The ultimate goal of this program is to achieve operational stability and compliance through asset risk control strategies that mitigate known risks. An example of an asset risk control strategy related to safety would be conducting predictive maintenance (e.g., vibration measurement and analysis) for a process cooling water circulation pump to ensure the pump does not unexpectedly fail and allow an exothermic process to overheat. This also has operational benefit through preventing the unexpected failure and associated downtime to repair the failed pump.

Figure 1. Key aspects of operational excellence.

Figure 2 outlines a process that starts with a list of site assets and progresses through creation of specific asset risk control strategies.

Establishing Impact Criteria and Methodology

In order to determine which assets are critical to the operation, impact criteria must be developed that specifically relate to the operation. Each asset will be evaluated for all categories chosen; therefore, the categories should be limited to allow for feasible execution, but still capture an accurate assessment of overall criticality.

Health, Safety and Environmental Criteria

Impact criteria that relate to personnel health and safety include a potential first aid injury, an OSHA recordable injury, a fatality or multiple fatalities. Environmental criteria can be categorized by potential on-site release/spill below Reportable Quantity (RQ), on-site contained release above RQ, uncontained release above RQ, release that affects vegetation or waterways off-site. Additional criteria for health, safety, and environmental impact assessment can be found within the published Center for Chemical Process Safety (CCPS) Guidelines for Risk Based Process Safety.

Quality Criteria

The *ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification* is an industry-recognized resource that provides criteria for determining potential impact to quality and is summarized as follows:

- Direct impact to quality:
  - The system has direct contact with the product (e.g., air quality)
  - The system provides an excipient or produces an ingredient or solvent (e.g., water for injection)
  - The system is used in cleaning or sterilizing (e.g., clean steam)
  - The system preserves product status (e.g., nitrogen)
  - The system produces data which is used to accept or reject product (e.g., electronic batch record system or critical process parameter chart recorder)
  - The system is a process control system (e.g., PLC, DCS) that may affect product quality and there is no system for independent verification of control system performance in place

- Indirect Impact to Quality:
  - The system supports a direct impact system or func-

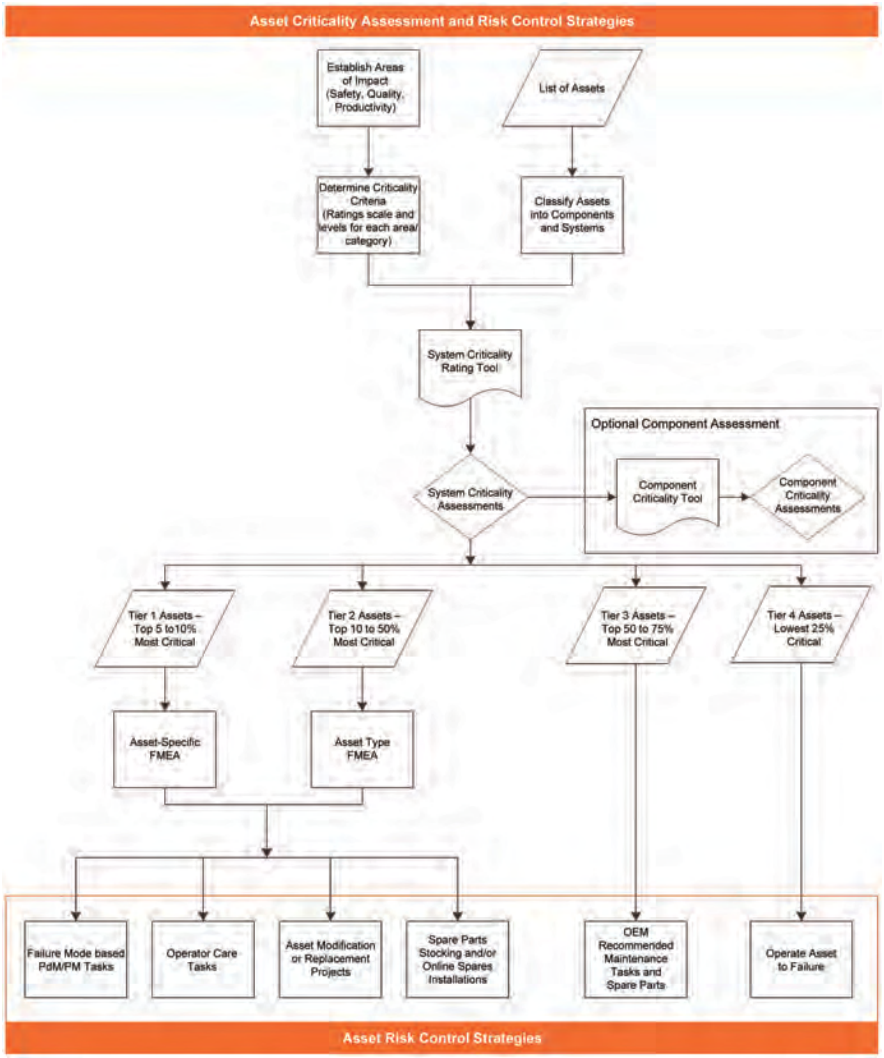


Figure 2. Process for managing risk through asset criticality assessments.

tion (e.g., tank jacket process cooling water)

- No Impact to Quality:
  - The system does not meet any of the criteria for direct or indirect impact to quality (e.g., administrative facilities)

Productivity Criteria

A thorough understanding of the operational value stream is required to determine the potential impact of an asset to productivity and the business. Specific stages of a process may include cost-intensive manufacturing steps or a significant quantity of product. Capturing the impact to the profit plan is the most direct measurement of business impact, based on actual monetized loss. For some operations, a significant impact to their profit may be $100,000, while for others a significant impact may be $10,000,000 or more.

Other Factors of Criticality

Customer Impact: the potential for a delayed delivery, loss of a sale, loss of a customer, or brand impact.

Strategic Plan Impact: an asset manufacturing or storing a product that is critical to the business strategy and long-range plan.

Asset Reliability: the failure rate of a specific asset categorized as one failure per day, week, month, quarter, year, etc.

Maintainability: the Mean Time To Repair (MTTR) an asset and put it back in service categorized as less than a day, several days, one week, several weeks, or possibly months. This category will factor in spare parts availability in addition to serviceability.

Utilization: establishing whether the asset is fully utilized 100% of available operating hours or only utilized 10% or less. Also, a specific functionality may be needed 100% during operation, but parallel assets (online spares) can reduce each individual asset to 50% or less utilized.

Single Point of Failure: identify whether or not the asset has a continuity or contingency plan in place.

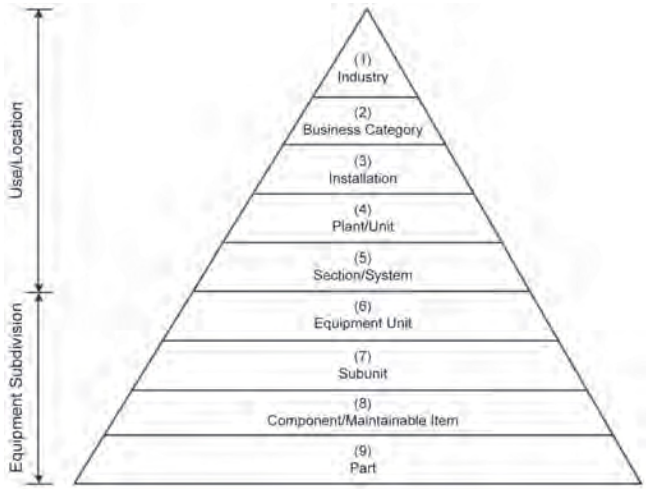


Figure 3. Taxonomy from ISO Standard 14224.

Replacement Cost: categorizing specific asset replacement costs to identify where unique technology and significant replacement risks exist within the value stream.

Decommissioning: biological compounds and allergens may require resource intensive decommissioning efforts and therefore present a higher risk to the operation.

Classifying Assets

It is most common to start with a list of all site assets from the Computerized Maintenance Management System (CMMS), the Enterprise Asset Management (EAM) system, or the financial system. Site walk-downs should be conducted to compare the asset listing and drawings to actual field conditions. Updating the asset listing at an early stage will allow for efficient use of time during subsequent criticality assessments.

While written for the petroleum and natural gas industries, ISO Standard 14224 provides relevant guidance for establishing asset taxonomy or relational structure. The most common structure is a parent-child hierarchy. At a minimum, the site should establish a list of lowest maintainable components (ISO 14224 Taxonomy Level 8), and group these into equipment units or subunits (ISO 14224 Taxonomy Level 6 and 7); reference Figure 3 for the complete pyramid of hierarchy levels. Most operations will have thousands of maintainable components, and combining these into several hundred groups of assets (systems) or less will allow for a more reasonable initial execution of criticality assessment.

Criticality Assessments

Conducting asset criticality assessments requires a spreadsheet or database tool that can combine the large list of assets and the category rating criteria. Also, averaging, weighting and sorting are key functional requirements of the rating tool as seen in Table A.

After uploading the list of assets to the rating tool, each category is considered for potential impact from a most probable failure mode, or set of failures. Catastrophic events such as natural disasters would typically not be considered during the analysis, but significant failures related to each asset should be. Asset safety devices, such as light beams, rupture disks, etc., should be taken into consideration by reducing the likelihood of occurrence. Similar to conducting a Process Hazard Analysis (PHA) for safety management

System Name	Description	Physical Location	CMMS Functional Location	HSE Impact	Health and Safety Impact	Environmental Impact	Quality Impact	Production Impact	Profit Impact	Customer Impact	Strategic Plan Impact	Reliability	Replacement Cost	Maintainability	Utilization	Raw Value	Criticality Ranking
Fermeter 1	Main Fermenter	Building 1	US-FL-MIA-B1-FTR-1	7	6	8	8	5	6	4	5	3	6	6	6	41	68
Filling Machine ABC	Aseptic Filling Machine	Fill Line A	US-FL-MIA-B1-FLR-A	6	9	2	10	10	10	10	10	8	10	8	8	60	100
Chilled Water	Site Chilled Water System	Utilities Bldg/Site	US-FL-MIA-UTL-CHW	3	2	3	5	3	4	3	1	2	8	2	10	33	55
Steam	Site Steam System	Utilities Bldg/Site	US-FL-MIA-UTL-STM	6	10	2	5	6	7	4	7	1	7	2	10	37	62
WFI Skid	Water for Injection Generation	Bldg 1 Penthouse	US-FL-MIA-B1-UTL-WFI	4	6	1	10	10	10	10	10	6	7	7	10	54	90
Wastewater Neutralization	Wastewater Treatment	Site	US-FL-MIA-UTL-WN	9	8	10	1	1	2	1	1	3	8	2	10	34	57
Admin HVAC	Administration HVAC	Building A	US-MIA-BA-AHU	1	1	1	1	1	1	1	1	1	3	1	10	18	30

Table A. Criticality assessment rating tool.

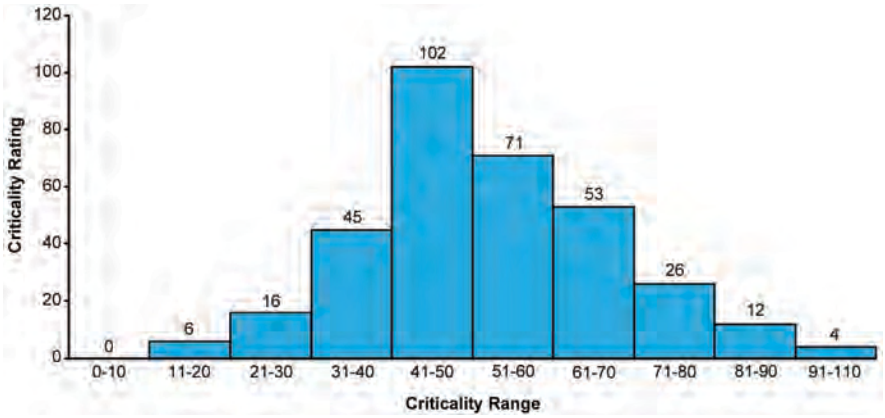


Figure 4. Criticality ratings distribution example.

programs, both the severity of impact and the likelihood of occurrence are factored together when assessing risk. If a numerical 1 to 10 scale is used within the rating tool, each category aligns criteria across this range. For example, the category of utilization may have a range as follows:

- 10 = 100% Utilized
- 9 = 90% Utilized
- 8 = 80% Utilized
- 7 = 70% Utilized
- 6 = 60% Utilized
- 5 = 50% Utilized
- 4 = 40% Utilized
- 3 = 30% Utilized
- 2 = 20% Utilized
- 1 = <10% Utilized

For quality impact ratings, the following may be used:

- 10 = Final Drug Product Direct Impact
- 8 = API Direct Impact
- 5 = Indirect Impact
- 1 = No Impact

Note: if your operation manufactures both API and final drug product, you may choose to have a lower level of impact for API direct impact systems, assuming there are purification steps at the beginning of final drug product processing. This elevates assets directly involved with final drug product manufacturing, where typically purity and sterility are of higher importance.

An alternative quality impact rating scale could incorporate potential impact of an asset on a product's critical quality attributes (e.g., safety, identity, strength, purity, quality). For example, if a system has the potential to introduce a contaminant or bioburden to the process that is not removed downstream, this could directly impact patient health. For this approach, the following is an example of quality impact ratings:

- 10 = Product contamination or lack of efficacy that could impact patient health
- 9 = Product contamination or lack of efficacy that would lead to internal (corporate supply chain) quarantine
- 8 = Repeat manufacturing deviation from validated process
- 7 = Manufacturing deviation from validated process
- 1 = No impact to quality

Note: with this rating scale, it may be appropriate to "weight" the criteria scores due to the extremely high impact potential on patient health and the business.

The goal of criticality rating is to obtain a balanced value across all impact criteria categories. Therefore, if several categories are related, they should be averaged as subcategories under a broader heading. For example, profit plan, customer impact, and strategic plan impact all relate to the overall business or productivity category, and are averaged in the example provided in Table A to provide one score for the production impact. Ultimately, each operation must decide what the category balance or weighting should be. Each of the main categories are then added or multiplied together to obtain a balanced criticality "raw value," and the final criticality ranking can be normalized to a 100 or 1,000 scale.

A best practice is to conduct criticality assessments for all assets at ISO 14224 Taxonomy Level 6 and 7, and then continue to evaluate each component level asset. This ensures that assets rated as non-critical or quality no impact, do not have any critical or quality direct impact components. It also identifies specific component-level assets that are highly critical to the overall operation, and therefore should have specific asset risk control strategies developed.

Creating Asset Risk Control Strategies

Upon completion of criticality assessments, a distribution of ratings typically resembles a bell curve or slightly skewed bell curve as seen in Figure 4.

Further grouping of the ranges into tiers pulls together groups of assets with similar criticality ratings:

- Tier 1 – Highly Critical: Top 5 to 10% of all rated assets
- Tier 2 – Moderately Critical: Top 10 to 50% of all rated assets
- Tier 3 – Low Critical: Top 50 to 75% of all rated assets
- Tier 4 – Non Critical: Lowest 25% of all rated assets

Separation of these tiers is required to assign an appropri-

ate level of additional analysis and the creation of asset risk control strategies. For highly critical assets, an asset-specific Failure Mode And Effects Analysis (FMEA) should be conducted to ensure all potential failure modes are evaluated, and that appropriate tasks are developed to address each failure mode. For moderately critical assets, a FMEA for each asset type should be conducted (e.g., centrifugal pumps, tanks, etc.). Each FMEA can produce the following risk control strategies:

- *Predictive Maintenance (PdM):* activities based upon a specific operating condition of the asset utilized to detect the onset of a failure prior to becoming a functional failure. These tasks would include risk-based inspections for mechanical integrity. An example of a PdM task is using infrared thermography to detect an abnormally hot air handler fan pulley due to belt drive misalignment.
- *Preventive Maintenance (PM):* activities scheduled to be completed based upon a specific time or run-rate interval regardless of the asset condition. An example is changing air handling unit belts every six months regardless of wear.
- *Operator Care:* tasks conducted by operators during normal production such as equipment inspection, lubrication, or cleaning.
- *Asset modification or replacement:* a project to modify the design of an asset or replace it with new functionality to mitigate known risks.
- *Spare parts stocking and/or online spares:* this would involve adjusting the site spare parts stocking requirements or potentially installing an online spare for continuity of service.

The risk control strategy most often adopted for low-critical assets is Original Equipment Manufacturer (OEM) recommended maintenance tasks. The effectiveness and level of control provided through these tasks must be evaluated to ensure it is appropriate with the rated criticality level.

For the non-critical lowest tier of assets, running the asset to failure is typically the appropriate strategy. However, specific review of potential safety, environmental or quality impact should be conducted to ensure these areas have an acceptable level of risk under this strategy.

Quality critical assets, regardless of tier, can be sorted and evaluated for additional operational and maintenance requirements. If an asset is determined to be overall non critical, but could have indirect impact to product SISPQ, post-maintenance requirements such as cleaning or sanitization may be appropriate. Also, management of change and Commissioning and Qualification (C&Q) procedures can reference the quality criticality rating for level of documentation and C&Q required.

Understanding Asset Criticality to Manage Risk

Risks to safety, quality and productivity are managed through asset risk control strategies, which are created based upon specific asset criticality and failure modes. High risks to all areas of the operation receive the most robust risk control strategies, while low-risk assets are run to failure. When risks to the operation are appropriately mitigated, unexpected production downtime is minimized. Building upon PSM and quality risk assessments by also evaluating the productivity impact is how to ensure all risks to the operation are understood and mitigated. A holistic risk-based asset management program improves operational stability and maximizes value from your physical assets, while also maintaining a high level of safety and quality compliance.

References

1. *ASTM E2500-07(2012): Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment,* www.astm.org.

2. *CCPS Guidelines for Risk Based Process Safety,* American Institute of Chemical Engineers (AIChE) Center for Chemical Process Safety (CCPS), March 2007, www.aiche.org/ccps.

3. *ISO 14224:2006: Petroleum, Petrochemical and Natural Gas Industries – Collection and Exchange of Reliability and Maintenance Data for Equipment,* www.iso.org.

4. *ISPE Baseline® Pharmaceutical Engineering Guide, Volume 5 – Commissioning and Qualification,* International Society for Pharmaceutical Engineering (ISPE), First Edition, March 2001, www.ispe.org.

About the Author

David J. Mierau, PE, CMRP is a licensed professional engineer and certified maintenance and reliability professional with a broad range of technical and management experience within the pharmaceutical and biotech industries. He is a member of ISPE and the Society for Maintenance and Reliability Professionals (SMRP). Mierau is currently a Senior Reliability Engineering Subject Matter Expert with Life Cycle Engineering providing asset management, reliability, root cause analysis, and engineering management consulting services. He can be reached at dmierau@LCE.com.

Life Cycle Engineering, 4360 Corporate Rd., Charleston, South Carolina 29405, USA.

WORLDWIDE. Raised blood pressure is estimated to cause 7.5 million deaths annually – about 12.8% of the total of all deaths. Raised blood pressure is a major risk factor for coronary heart disease and stroke.

CHINA. AstraZeneca is building a new facility for production of oral solid dosage products, including Betaloc, which is used to treat high blood pressure.

nne pharmaplan®

Engineering for a healthier world

Student Poster Winner

To Investigate the Antimicrobial Potential of *Lucilia sericata* Larvae

by Qin Xiang Ng

This article presents a research project that investigates the antimicrobial effects of excretions/secretions and gas flatulence produced by *Lucilia sericata* larvae on *Escherichia coli*, *Staphylococcus epidermidis,* and *Micrococcus luteus*. It was presented at the 2013 ISPE Annual Meeting as part of the student poster competition.

According to a study done by the Center for Disease Control and Prevention (CDC) in the United States alone, food-borne diseases account for 76 million diseases, 325,000 hospitalizations, and 5,000 deaths each year;[1] and bacterial infections make up for approximately 5 million of these diseases.[1]

Modern medicine depends heavily on the use of antibiotics to kill pathogenic bacteria. Antibiotics are classified according to their structure and mechanism of action, e.g., the inhibition of metabolic processes which are vital for bacterial growth and replication. The main mechanisms of antibiotics are inhibition of cell wall, protein, important enzymes, nucleic acid synthesis and disruption of cell membrane;[2] however, in the recent years, the emergence of antibiotic-resistant bacteria (superbugs) has become a global concern as these "superbugs" are resistant to even the most powerful of modern antibiotics.[3]

Worryingly, there has not been a new class of antibiotics discovered since the 1980s.[4] The World Health Organization (WHO) has warned that the world is heading toward a "post-antibiotic era" and "many common infections will no longer have a cure and, once again, could kill unabated."[4]

The limitations of antibiotic treatment and the rapid emergence of antibiotic-resistant pathogenic bacteria have renewed interest in efforts to find alternative antimicrobial therapeutics. Maggot Debridement Therapy (MDT) is an unconventional therapeutic treatment involving the introduction of live, sterile larvae into the non-healing skin and soft tissue wounds of a patient for the purpose of cleaning out the necrotic tissue within a wound and disinfection. Maggot debridement therapy is reportedly effective for wounds infected by methicillin-resistant Staphylococcus aureus (MRSA) and "flesh-eating bacteria."[5] As limited studies have been done to investigate the exact antiseptic mechanisms, this project aimed to investigate the antimicrobial effects of excretions/secretions and gas flatulence produced by *Lucilia sericata* larvae on *Escherichia coli, Staphylococcus epidermidis*, and *Micrococcus luteus*.

Materials and Methods

Lucilia sericata larvae were reared on a diet of ad libitum pig's liver; third-instar larvae (three-day-old) were used for all experiments. Briefly, overnight Excretions/Secretions (ES) were collected from 10 g of third-instar larvae, centrifuged to remove particulate material and filter-sterilized before use. 1000 µl of 10^3 colony forming units (cfu)/ml bacterial broth culture was combined with 100 µl of sterile ES extract, antibiotic ampicillin or sterile water. Subsequently, 10 µl of the mixture was plated onto a new sterile Luria Bertani (LB) agar plate for enumeration of bacterial colonies after overnight incubation at 37°C.

To investigate the possible antimicrobial effects of larval flatulence, an air-tight setup was constructed. The entire experiment was carried out within a laminar flow hood to ensure sterility. Gas flatulence produced by 500 third-instar

larvae was applied to bacterial culture plates (plated with 10 µl of 10^3 cfu/ml of *E. coli, S. epidermidis,* or *M. luteus*) and an accompanying control plate (with no bacteria plated) for an hour. Unidirectional flow of air was ensured by using a suction pump set at 80 Pa. The plates were then removed from the exposure box and incubated overnight at 37°C for enumeration of bacterial colonies.

Results and Discussion

As seen in Figure 1, the larval excretions/secretions showed significant inhibitory effects against both Gram-positive and Gram-negative bacteria tested in this study. When compared to the control (sterile water), the difference in the average number of bacterial colonies counted was confirmed to be significant using two-tailed unpaired t-test. Furthermore, we can see that the antimicrobial effects of larval excretions/secretions were comparable to that of ampicillin (30 mcg/ml); in fact, it exhibited a more pronounced antimicrobial effect against *S. epidermidis* than ampicillin, causing a remarkable 89.21% decrease in the number of *S. epidermidis* colonies as compared to the control.

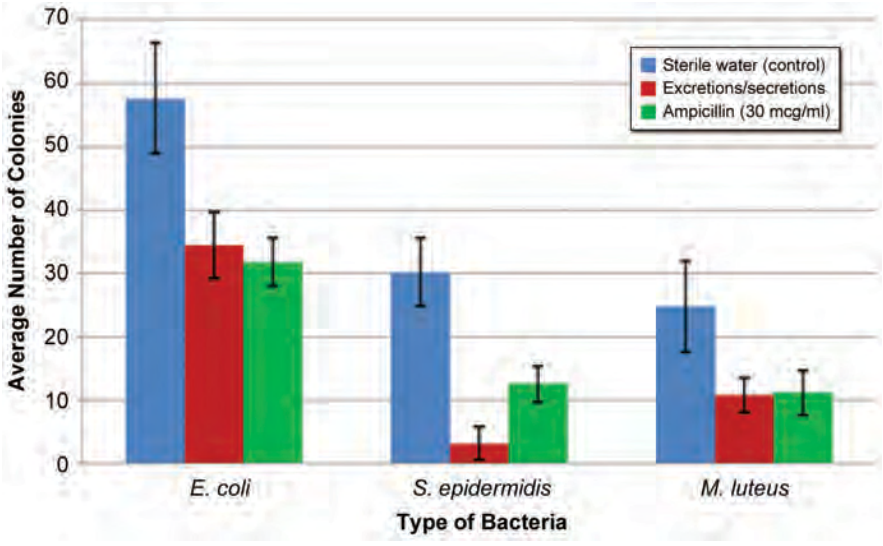


Figure 1. Antimicrobial effects of larval excretions/secretions on *E. coli, S. epidermidis,* and *M. luteus* (error bars showing ±1 standard deviation, n = 30).

The larval excretions/secretions were tested with a pH probe and showed to be alkaline in nature (pH 9). Its antibacterial effects and alkaline nature can be attributed to the presence of ammonia, ammonium bicarbonate, urea, allantoin and various proteolytic enzymes, e.g., chymotrypsins.[6]

As for the larval flatulence, it also has significant antimicrobial properties when comparing the average number of bacterial colonies counted to the control setups (i.e., $p < 0.05$). This can be seen in Figure 2. Two controls were used in this experiment. As the larval maggots were fed with pig's liver, another control setup was prepared with just pig's liver and no maggots present to rule out the effect of any gases that may be released by microorganisms found in the non-sterile pig's liver.

Preliminary chemical analysis of the gas flatulence has been done using gas chromatography-mass spectrometry (GC-MS) and results showed that compounds like aldehydes, aliphatic esters, ethers, ketones, phenols and derivatives, alcohol and siloxane are present in the flatulence produced by the larvae. The presence of these organic compounds creates an environment unfavourable for bacterial growth as some of them are bactericidal in nature. However, 28% of the compounds remain unidentified. GC-MS is also unable to analyse non-volatile and thermally fragile compounds, further analysis should be done using HPLC-MS.

Conclusion

In conclusion, the results showed that natural products from *L. sericata* larvae hold great promise for development of potent antimicrobial therapeutics.

The larval excretions/secretions, being liquids, could be

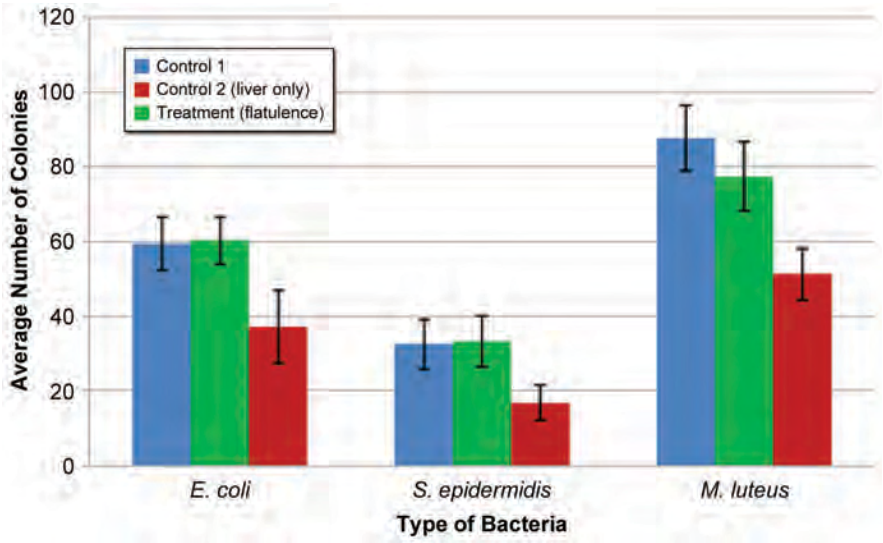


Figure 2. Antimicrobial effects of larval flatulence on *E. coli, S. epidermidis,* and *M. luteus* (error bars showing ±1 standard deviation, n = 30).

freeze-dried to prolong its shelf life. And these larval excretions/secretions could be further analyzed using high-performance liquid chromatography to identify and isolate the bioactive compounds present.

The gas flatulence could be further refined and made into an inhalant for treating lung infections, such as tuberculosis, a terrible disease that affects an estimated one third of the world's population, with new infections occurring at a rate of about one per second.[7] Antibiotic resistance is a growing problem in Multiple Drug-Resistant Tuberculosis (MDR-TB) infections. Normally, tuberculosis is treated using oral antibiotics and there is no targeted delivery. If the larval flatulence is made into an inhalant, targeted delivery is possible as the medication is directed straight to the lungs. Gases and volatile drugs may be inhaled and absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract. Access to the systemic circulation is rapid by this route because the lung's surface area is large (pulmonary absorption is rapid) and first-pass metabolism by the hepatobiliary system is avoided.[8]

Future work entails testing the larval excretions/secretions and flatulence on a greater variety of bacteria, particularly antibiotic-resistant strains, and further chemical analyses of these natural products. In addition, for an antimicrobial agent to be considered effective, not only must it possess good antibacterial efficacy, it also must be selectively toxic. Being selectively toxic means that they must target only the disease-causing bacteria and have minimal or no toxicity to the host cells. Hence, the possible cytotoxic and genotoxic effects of the proposed treatment methods also must be evaluated (by testing on human cell lines so as to ensure that these natural products are safe for oral consumption or topical application).

Also, previous studies have suggested that excretions/secretions from aseptically raised larvae were much less potent than those collected from non-sterile maggots.9 This is an exciting area for future study as this possibly implies that the antimicrobial efficacy of these extracts (and maggot therapy) can be enhanced by pre-inoculating larvae with non-pathogenic strains of antibiotic-resistant bacteria in order to prime the gut with antimicrobials.

References

1. Mead, P.S., Slutsker, L., Dietz, V., McCaig, L.F., Bresee, J.S., Shapiro, C., and Tauxe, R.V,. "Food-related Illness and Death in the United States," *Emerging infectious diseases,* 1999, 5(5), 607.

2. Walsh, C. "Antibiotics: Actions, Origins, Resistance," *American Society for Microbiology (ASM),* 2003.

3. Ferber, D., "Superbugs on the Hoof?" *Science,* 2000, 288(5467), 792-794.

4. Gallagher, J., " Analysis: Antibiotic Apocalypse," *BBC News Health and Science,* 2013.

5. Chan, D.C., Fong, D.H., Leung, J.Y., Patil, N.G., and Leung, G.K., "Maggot Debridement Therapy in Chronic Wound Care," *Hong Kong Medical Journal,* 2007, 13 (5), 382.

6. Parnes, A., and Lagan, K.M., " Larval Therapy in Wound Management: A Review," *International Journal of Clinical Practice,* 2007, 61(3), 488-493.

7. Caminero, J.A., "Multidrug-resistant Tuberculosis: Epidemiology, Risk Factors and Case Finding," *The International Journal of Tuberculosis and Lung Disease: the Official Journal of the International Union Against Tuberculosis and Lung Disease,* 2010, 14(4), 382-390.

8. Rang, H.P., and Dale, M.M., *Rang and Dale's Pharmacology,* Elsevier Brasil, 2007.

9. Sherman, R.A., Hall, M.J.R., and Thomas, S., "Medicinal Maggots: An Ancient Remedy for Some Contemporary Afflictions, *Annual Review of Entomology,* 2000, 45(1), 55-81.

About the Author

Qin Xiang Ng, a graduate of the International Baccalaureate (IB) program, he is currently a second-year medical student at the Yong Loo Lin School of Medicine, National University of Singapore. He is due to graduate with a Bachelor of Medicine, Bachelor of Surgery (M.B., B.S.) by 2017. Besides being a member of the ISPE, he is also an active member of the Singapore Medical Association (SMA), Singapore Society of Cosmetic Scientists, Singapore Academy of Young Engineers and Scientists (SAYES), Society for Science and the Public (SSP), and the Anglo-Chinese School Old Boy's Association (ACS OBA). He has distinguished himself as an excellent young scientist, having received numerous national and international science awards. These include Second Place at the INTEL International Science and Engineering Fair (INTEL-ISEF) 2011, the WSPC-ICAAS Most Outstanding Junior College Science Student Award and the A*STAR Science Award. He can be contacted by tel: +65-91251908 or email: a0105940@nus.edu.sg.

National University of Singapore – Yong Loo Lin School of Medicine, 21 Lower Kent Ridge Rd., 119077, Singapore.

PharmEng Technology

COMPLIANCE ↑

Rapid Response cGMP Compliance

PharmEng has been serving the regulated life science industry for over 15 years. Our expertise involve current regulatory practices from around the globe. We provide services to the manufacturers of pharmaceuticals, biotech products, medical devices, nutraceuticals and supply chain functions to numerous clients.

Our team of highly qualified specialists are assembled from various disciplines to meet all your project needs. We provide cost-effective and timely solutions proven to deliver exceptional results. Working collaboratively with our clients' personnel, we ensure a cooperative relationship that maximizes productivity and efficiency. By delivering quality in every facet of our services, ensures our success through your satisfaction.

Our Services

- ✔ Project Management
- ✔ Quality Systems
- ✔ Validation (C&Q)
- ✔ Regulatory Affairs
- ✔ Engineering
- ✔ Training
- ✔ Information Technology

Our Advantage cGMP Compliance

- ✔ Consent Decree
- ✔ FDA 483 Warning Letters
- ✔ Pre-FDA Inspections
- ✔ Audits
- ✔ Serialisation

Worldwide Offices

Toll Free: 1.855.YES.CGXP
USA: 919.474.8309
Canada: 416.385.3922 ext. 103
Asia: +65.68365524

Contact us at **info@pharmeng.com** or
Visit us at **www.pharmeng.com**

Scan with your Smart Phone to learn more about PharmEng

Certified System ISO 9001

CERTIFIED SUPPLIER CAMSC

NMSDC

Global Regulatory News

International

U.S. Regulator on India Visit Calls for Greater Drug Safety Collaboration[1]

The head of the U.S. Food and Drug Administration (FDA) called for more collaboration among regulators to improve drug quality and safety as she wrapped up a visit to India after recent import bans on drugs from a handful of plants in the country.

FDA and European Medicines Agency Strengthen Collaboration in Pharmacovigilance Area[2]

The U.S. FDA and the European Medicines Agency (EMA) have set-up a new "cluster" on pharmacovigilance topics. Clusters are regular collaborative meetings between the EMA and regulators outside of the European Union, which focus on specific topic areas that have been identified as requiring an intensified exchange of information and collaboration. Building on the experience of previous regular videoconferences between the FDA and the EMA in this area and on the recent creation of the EMA's Pharmacovigilance Risk Assessment Committee, this cluster will provide a forum or a more systematic and focused exchange of information on the safety of medicines.

FDA-EMA Extends Pilot Program of the QbD Parallel-Assessment[3]

The FDA and the EMA have agreed on a two-year extension of the joint pilot program for the parallel evaluation of Quality by Design (QbD) applications beginning 1 April 2014. The FDA and EMA began the joint venture in March, 2011 to share knowledge, ensure consistent adherence to international guidelines related to QbD and promote the availability of pharmaceutical products of consistent quality throughout the European Union and the U.S. QbD is an approach to ensuring consistent drug quality through statistical, analytical and risk-management methodology in drug design, development and manufacturing.

First Australia/New Zealand Harmonization Activity Completed[4]

New Zealand has changed paediatric dosage instructions for paracetamol and ibuprofen to align with Australia.

The Nordic Medicinal Agencies Release Guidance on Nordic Packages[5]

These documents apply to medicinal products for both human and veterinary use. The Guideline on Nordic Packages document contains general information on Nordic packages, whereas the Frequently Asked Questions document gives detailed advice on different package issues. Marketing authorization holders may submit questions regarding issues relating to Nordic packages. For this purpose a specific form, Question to the Nordic package group, is published and should be used. The documents are a product of cooperation between the Medicines Agencies in Denmark, Finland, Iceland, Norway, and Sweden.

Accord between Argentina and Caribbean Countries Leads to Stronger Drug Regulatory Capacity[6]

A cooperation agreement between Argentina's drug regulatory authority, NMAT, and regulatory authorities of Jamaica, Trinidad and Tobago, Guyana and Suriname has led to improved capacity in the Caribbean countries for control of medicines. The accord was supported by the Pan American Health Organization/World Health Organization (PAHO/WHO).

Publication "Drug Regulatory PALOPs"[7]

The purpose of this publication is the dissemination of regulated information of all pharmaceutical African Portuguese Speaking Countries (PALOP) by compiling, in a systematic way, each of the respective national systems for regulating the pharmaceutical area. This project resulted from collaboration between several entities: the Infarmed IP, representatives of regulatory agencies PSAC, the Phagecon - Services and Consulting Pharmaceuticals Ltd, with the support of APIFARMA and Pharma Portugal.

PIC/S

Revised PIC/S GMP Guide[8]

The PIC/S Committee has adopted by written procedure the revision of the PIC/S GMP Guide (PE 009-11). The revised GMP Guide entered into force on 1 March 2014. The following parts have been amended:

- Part II of GMP Guide (Q7A): introduction of risk management principles
- Annex 2 (biological medicinal products for human use)
- Annex 14 (products derived from human blood or human plasma)

Hans Smallenbroek, Founding Father of PIC/S, Passes Away[9]

Hans Smallenbroek, one of the founding fathers of the PIC Scheme (PIC/S), died on 19 March 2014 – only three days before his 63th birthday.

Asia/Pacific

Australia

Fifty years of Independent Expert Advice on Prescription Medicines[10]

The Therapeutic Goods Administration has published a document chronicling the history of the Advisory Committee on Prescription Medicine, and how it has used independent expert advice to protect public health. The document can be found at: http://www.tga.gov.au/about/committees-pm-50years.htm#.Uwzei_ldXuw.

Upgraded Over-the-Counter Medicines Online Application System[11]

From 9 April 2014, over-the-counter medicines applications will be submitted through an upgrade to the OTC medicines online application system. Applications will be easier to submit and process and industry will benefit from this reduction in regulatory burden.

Streamlining and Improving Therapeutic Goods Legislation[12]

The Therapeutic Goods Administration published new amendments which include a number of minor, but important changes that streamline and improve the operation of the regulatory scheme for industry, consumers, health professionals and the TGA. These changes ensure greater consistency in the regulation of different types of therapeutic goods.

China

CFDA Issues Special Review and Approval Procedure for Innovative Medical Devices[13]

On 7 February 2014, the China Food and Drug Administration (CFDA) issued the Special Review and Approval Procedure for Innovative Medical Devices (interim), which was put into force on 1 March 2014. The Procedure is an approval channel for innovative medical devices under the precondition of ensuring the safety and effectiveness of marketed products.

The State Council Passes the Draft Amendment to the Regulations for the Supervision and Administration of Medical Devices[14]

The draft amendment to the Regulations for the Supervision and Administration of Medical Devices was adopted at the executive meeting of

the State Council on 12 February 2014, and will be promulgated and implemented soon.

After the comprehensive revision to the original Regulations, the draft amendment to the Regulations consists of 80 articles in eight chapters. The draft amendment adjusted the definition and classification rules of medical devices; further improved the authority management for product registration, approval or record keeping of manufacturing and distribution of medical devices; set up measures for quality supervision and risk control during the manufacturing of medical devices; established systems for adverse event monitoring, tracing and recall of medical devices; further strengthened inventory management, examination and acceptance system, and certificate claim in the distribution of medical devices; added relevant requirements on supervision of the medical devices in use; and increased the punishments for illegal activities.

Japan

MHLW Implements Supplement II to the Japanese Pharmacopeia Sixteenth Edition[15]

Supplement II to the Japanese Pharmacopeia Sixteenth Edition can be found at: http://www.pmda.go.jp/english/pharmacopoeia/online.html.

Korea

Korea Amends Enforcement Regulations of the Medical Device Act[16]

Previously, when medical device distributors or lessors wished to purchase medical devices from medical institutions, medical devices were possible to be sold or leased out after their compliance with good manufacturing practices or quality management system was verified by the manufacture or importer. However, the amended enforcement regulations are relaxed so that tests can be done by medical device test institutions designated by the Minister of the Food and Drug Safety.

Europe

European Union

European Medicines Agency Introduces Unique Product Identifiers (UPIs)[17]

Companies that approach the Agency for the first time with a new medicine, whether this is for an orphan designation, a procedure related to paediatric development, or a scientific advice procedure, will need to complete a registration form to provide simple information on the medicine and send it to upiregistration@ema.europa.eu in order to receive their UPI. Companies will then need to use this UPI every time they contact the Agency for any matter related to this specific medicine.

Rare Disease Day 2014 – Twelve New Orphan Medicines Available to Patients[18]

Over the past 12 months, a total of 12 medicines for the treatment of rare diseases were recommended for marketing authorization by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP). They include medicines for the treatment of rare cancers (3), multidrug resistant tuberculosis (3) and pulmonary arterial hypertension (2). About 30 million people living in the European Union (EU) suffer from a rare disease, which is a condition that does not affect more than five in 10,000 people.

European Medicines Agency Welcomes New Head of IT Development Department[19]

Dina Tsiambaou joins the European Medicines Agency (EMA) as the new Head of IT Development Department in the Information Technology Division. Tsiambaou comes to the Agency from her role as Senior Manager at Accenture, where she had a long career defining, leading and delivering complex IT transformation and implementation projects. A Greek national and B.Sc. graduate in computing in business from Brunel University in London, Tsiambaou holds extensive leadership experience, across different industries.

Committee for Advanced Therapies Elects New Chair[20]

The committee elected Dr Salmikangas as new chair for a three-year mandate at its February 2014 meeting. She succeeds Christian Schneider, who had chaired the committee since its creation in 2009. A Finnish national, Paula Salmikangas has qualifications in biochemistry and in cell and molecular biology. She has been senior researcher at the Finnish Medicines Agency since 2003. She was previously the vice-chair of the CAT, a position she held since the establishment of the committee.

Revision of European Commission Guidelines on Good Manufacturing Practice for Medicinal Products[21]

The European Commission has launched the public consultation on the revision of Annex 15: Qualification and Validation. This Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products. It is a GMP requirement that manufacturer's control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed. Computerized systems used for the manufacture of medicinal products should be validated according to the requirements of Annex 11. The relevant concepts and guidance presented in ICH Q8, Q10 and Q11 also should be taken into account.

European Medicines Agency Publishes First Summary of a Risk-Management Plan for a Medicine[22]

The European Medicines Agency has published the first summary for the public of the Risk Management Plan (RMP) of a newly authorized medicine. This RMP summary, which concerns the medicine Neuraceq, describes what is known and not known about the medicine's safety and states what measures will be taken to prevent or minimize its risks. The Agency will pilot the publishing of RMP summaries for all newly centrally authorized medicines during 2014 and at a later stage will start producing RMP summaries for previously authorized medicines.

Netherlands

Hurts Appointed New Director/ Secretary of the Medicines Evaluation Board[23]

As of 1 June 2014, Mr H.R. (Hugo) Hurts MSc will be the new Director/ Secretary of the Medicines Evaluation Board. Currently, Hurts is Director of Medicines and Medical Technology for the Ministry of Health, Welfare and Sport. He is an economist, and has previously held a variety of positions with the Ministry of Health, Welfare and Sport, including the position of director of Health Care Insurance.

United Kingdom

MHRA Appoints New Clinical Director of Medical Devices[24]

The Medicines and Healthcare products Regulatory Agency (MHRA) has appointed Dr Neil McGuire as its new Clinical Director of Medical Devices effective from 3 March 2014. Dr McGuire joins the MHRA from the Royal Air Force Medical Service and the Defence Medical Services where he was a Defence Consultant Adviser in anaesthesia, pain medicine and critical care and latterly the RAF's Medical Service Senior Consultant and a Queen's Honorary Surgeon.

The British Pharmacopoeia Celebrates its 150th Birthday[25]

The authoritative collection of medicinal standards, the British Pharmacopoeia (BP) turns 150 years old this week. The BP has a long and prestigious history which will be celebrated throughout 2014. The BP has evolved since its first edition was published in 1864. At this time, the London, Edinburgh and Dublin Pharmacopoeias were consolidated into one publication to form the first edition of the British Pharmacopoeia. This was a huge feat of harmonization and the work produced has evolved to become one of the most recognized and well respected reference books in the UK. The 2014 British Pharmacopoeia con-

tinues to be a successful business and is used and referenced in more than 100 countries.

Explanation of Medicines and Medical Devices Regulatory Systems is Published[26]

The article, entitled "Regulation of Medicines and Medical Devices: Contrasts and Similarities," provides a comprehensive overview of the regulatory process for medicines and medical devices. It can be found at http://www.clinmed.rcpjournal.org/content/14/1/6.full.pdf+html.

Annual Report on Regulation of Medicines Advertising Published[27]

The MHRA has published an annual report, "Delivering High Standards in Medicines Advertising Regulation," covering the year 2013. It provides details of the activities of the Advertising Standards Unit, including vetting of advertising and complaints investigated, and the development of guidance with self-regulatory bodies to promote high standards.

MHRA Publishes Guidance on Medical Device Stand-Alone Software[28]

This guidance is aimed at those working in healthcare and people who are developing devices. This is a constantly developing field and this guidance aims to:

- Outline the current regulatory position
- Explain what defines a medical device
- Help with decisions on whether your stand -alone software or app is a medical device and give examples
- Give information about the rules on classification of medical devices and how to meet the regulations
- Give links to other useful websites and relevant documents

North America

Canada

Good Manufacturing Practice (GMP) Guidelines for Active Pharmaceutical Ingredients (APIs) – (GUI-0104)[29]

These Good Manufacturing Practices (GMPs) for Active Pharmaceutical Ingredients (APIs) guidelines, GUI-0104, are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements. It should be noted that these guidelines do not cover safety aspects for the personnel engaged in the fabrication, packaging/labelling, and testing of APIs and intermediates, or aspects of protection of the environment. These controls are inherent responsibilities of the API fabricator, packager/labeller and tester.

United States

CDRH 2014 Strategic Priorities[30]

The Center for Devices and Radiological Health's (CDRH) 2014-2015 Strategic Priorities describe the most important areas that we will focus on because they are critical to reaching our vision. These priorities are:

- Strengthen the clinical trials enterprise
- Strike the right balance between premarket and postmarket data collection
- Provide excellent customer service

Draft Guidance for Industry on New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products[31]

This draft guidance sets forth a change in the Agency's interpretation of the five-year New Chemical Entity (NCE) exclusivity statutory and regulatory provisions as they apply to certain fixed-combination drug products (fixed combinations). If the guidance is finalized, a drug product will be eligible for five-year NCE exclusivity if it contains a drug substance that meets the definition of "new chemical entity," regardless of whether that drug substance is approved alone or in certain fixed-combinations.

Guidance for Industry: International Conference on Harmonization; E2B(R3) Electronic Transmission of Individual Case Safety Reports; Data Elements and Message Specification; Appendix on Backward and Forward Compatibility[32]

The E2B(R3) implementation guidance is intended to revise the standards for submission of ICSRs and improve the inherent quality of the data, enabling improved handling and analysis of ICSR reports. The BFC appendix describes the relationship between data elements from the 2001 ICH E2B guidance and the E2B(R3) implementation guidance.

Draft Guidance for Industry on Analytical Procedures and Methods Validation for Drugs and Biologics[33]

This revised draft guidance supersedes the 2000 draft guidance for industry on "Analytical Procedures and Methods Validation" and when finalized, will also replace the 1987 FDA guidance for industry on "Submitting Samples and Analytical Data for Methods Validation." This draft guidance discusses how to submit analytical procedures and methods validation data to support the documentation of the identity, strength, quality, purity, and potency of drug substances and drug products.

FDA Seeks to Modernize Over-the Counter Drug Reviews[34]

The U.S. FDA is proposing sweeping changes to how it regulates over-the-counter drugs from aspirin to allergy medications to make it easier to react to new information on a product's safety or recommended use. The Agency's current rules for nonprescription medicines are more than 40 years old,

and do not require manufacturers to get approval as long as the main ingredient had previously been deemed safe and effective for that entire category of medications. They do not allow the Agency to respond quickly when new data emerges about a drug's potential side effects, the Agency said in documents filed for the proposal.

Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff Guidance for Industry and Food and Drug Administration Staff[35]

The purpose of this guidance is to provide an overview of the mechanisms available to applicants through which they can request feedback from the U.S. FDA regarding potential or planned medical device investigational device exemption applications or other premarket submissions, such as Premarket Approval (PMA) applications, Humanitarian Device Exemption (HDE) applications, evaluation of automatic Class III designations (de novo petitions), premarket notification (510(k)) submissions, Clinical Laboratory Improvement Amendments (CLIA) Waiver by Application, and including certain Investigational New Drug Applications (INDs) and Biologics License Applications (BLAs). This guidance provides information regarding the logistics for submission, receipt, tracking, and review of/response to these requests.

FDA Initiates the Secure Supply Chain Pilot Program[36]

The U.S. FDA has initiated the Secure Supply Chain Pilot Program to enhance the security of imported drugs. In August 2013, the FDA published a notice in the Federal Register (78 FR 51192) to solicit companies to voluntarily submit applications for participation in this two-year program. Thirteen prequalified companies have now been designated to take part, and will receive expedited entry for the importation of up to five selected drug products into the United States.

The goal of the program is to enable the FDA to evaluate resource savings that will allow the Agency to focus imports surveillance resources on preventing the entry of high-risk drugs that are the most likely to compromise the quality and safety of the U.S. drug supply.

Exporting Medical Devices[37]

The rules that companies must follow

when exporting medical devices depend on whether or not their devices have been approved or cleared by the U.S. FDA. More information on these rules can be found at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ImportingandExportingDevices/ExportingMedicalDevices/default.htm.

Guidance for Industry Distributing Scientific and Medical Publications on Unapproved New Uses[38]

In 2009, the U.S. FDA issued a guidance titled Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (2009 guidance) to provide guidance on manufacturer distribution of "journal articles" and "scientific or medical reference publications." The FDA is revising its 2009 guidance on good reprint practices to clarify the Agency's position on manufacturer dissemination of scientific or medical reference texts and CPGs that include information on unapproved new uses of the manufacturer's products. New explanatory sections have been included on these topics. This revised draft guidance is being issued to enable the public to provide comments.

Why FDA Supports a Flexible Approach to Drug Development[39]

In a blog post, FDA Commissioner Margaret Hamburg discusses the value of adopting a flexible approach to drug development. She states, "Increased flexibility does not mean abandoning standards, and it certainly does not mean abandoning science. Just the opposite. We need to employ the best science in ways that will increase efficiency, productivity and our shared ability to find creative solutions to the challenges that confront us."

FY 2013 Report From the Director CBER[40]

In CBER's Fiscal Year 2013 Report, it is conveyed that CBER made important new healthcare products available to the public during fiscal year 2013 through timely review of many investigational applications for biologics and devices and the approval of many marketing applications.

What's New in the FDA's 2015 budget?[41]

Despite tight budgetary times, the President is requesting a $4.7 billion budget for the FDA, an 8.1 percent increase over the 2014 budget that Congress passed earlier this year. Most of the $61 million increase for medical product safety comes from increases that were written into the statute when Congress authorized each of the five-year user fee programs

Draft Guidance for Industry on Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products[42]

This guidance clarifies the FDA requirements and regulations pertaining to allowable excess volume in injectable vials and reinforces the importance of appropriate packaging sizes for injectable drug and biological products.

Draft Guidance for Industry on Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway[43]

This draft guidance discusses FDA's recommendations for developing the indication and usage statements in the prescribing information for drugs approved under the accelerated approval regulatory pathway (hereafter "accelerated approval"). The guidance also discusses labeling considerations for indications approved under accelerated approval when clinical benefit has been verified and FDA terminates the conditions of accelerated approval, or when FDA withdraws accelerated approval of an indication while other indications for the drug remain approved.

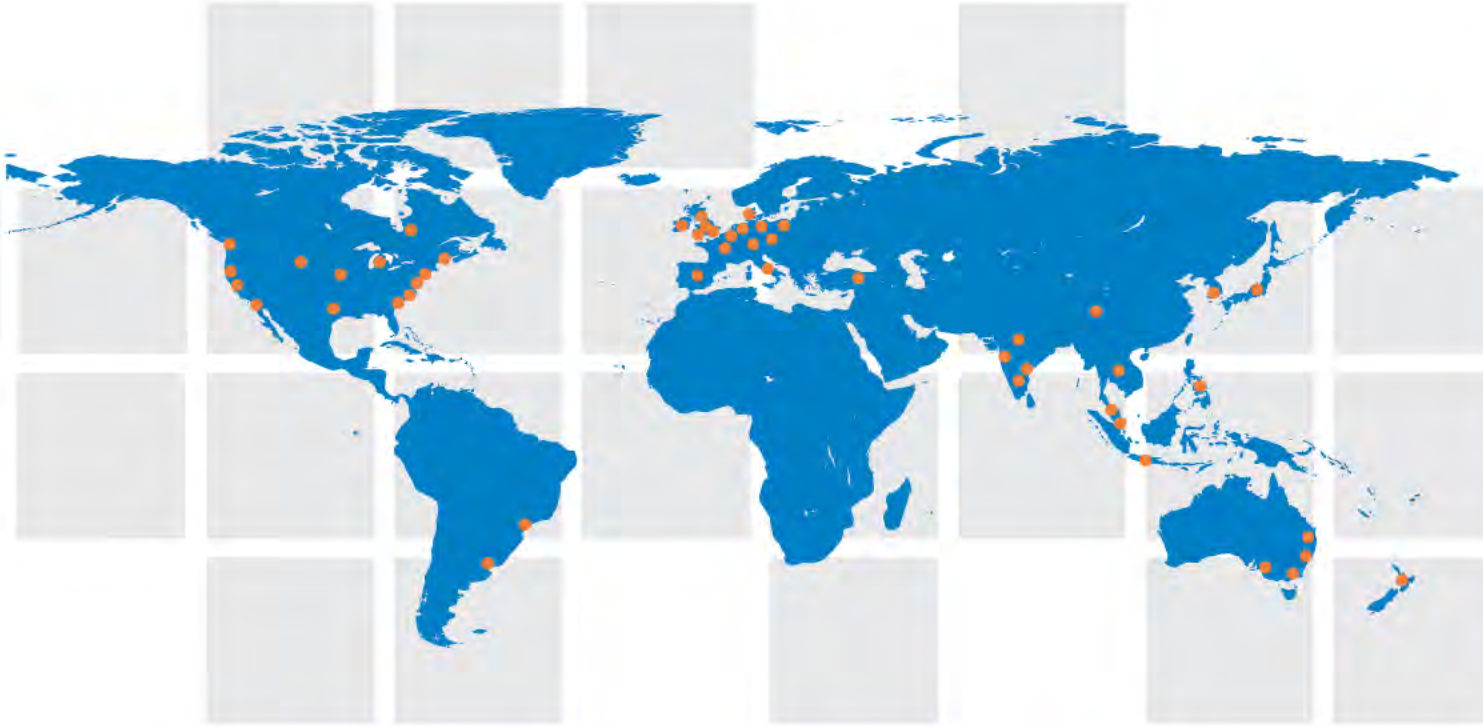
References

1. Reuters, http://www.reuters.com/article/2014/02/18/fda-hamburg-india-idUSL3N0LN38W20140218.
2. US Food and Drug Administration, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm386372.htm.
3. US Food and Drug Administration, http://www.fda.gov/Drugs/DrugSafety/ucm388009.htm.
4. Australian Therapeutic Goods Administration, http://www.tga.gov.au/newsroom/media-2014-harmonisation-activities-140212.htm#.UwzezvldXuw.
5. Swedish Medical Products Agency, http://www.lakemedelsverket.se/english/All-news/NYHETER-2014/The-Nordic-Medicinal-Agencies-release-Guidance-on-Nordic-packages.
6. Pan American Health Organization, http://www.paho.org/hq/index.php?option=com_content&view=article&id=9326%3Aacuerdo-entre-argentina-y-paises-del-caribe-avanza-en-el-fortalecimiento-de-control-de-medicamentos&catid=1443%3Anews-front-page-items&lang=en&Itemid=1926.
7. Portuguese National Authority of Medicine and Health Products, http://www.infarmed.pt/portal/page/portal/INFARMED/MAIS_NOVIDADES/DETALHE_NOVIDADE?itemid=9697029.
8. PIC/S, http://picscheme.org/news.php.
9. PIC/S, http://picscheme.org/news-detail.php?id=62.
10. Australian Therapeutic Goods Administration, http://www.tga.gov.au/about/committees-pm-50years.htm#.Uwzei_ldXuw.
11. Australian Therapeutic Goods Administration, http://www.tga.

gov.au/newsroom/media-2014-otc-online-140307.htm#.Ux8fF_ldXuw.
12. Australian Therapeutic Goods Administration, http://www.tga.gov.au/newsroom/media-2014-streamlining-leg-140324.htm#.UzBR9fldXuw.
13. China Food and Drug Administration, http://eng.sfda.gov.cn/WS03/CL0757/96724.html.
14. China Food and Drug Administration, http://eng.sfda.gov.cn/WS03/CL0757/96865.html.
15. Japanese Pharmaceticals and Medical Devices Agency, http://www.pmda.go.jp/english/pharmacopoeia/online.html.
16. Korean Food and Drug Administration, http://www.kfda.go.kr/eng/index.do?boardSeq=68675&mode=view&nMenuCode=15&s.
17. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/02/news_detail_002021.jsp&mid=WC0b01ac058004d5c1.
18. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/02/news_detail_002033.jsp&mid=WC0b01ac058004d5c1.
19. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/02/news_detail_002026.jsp&mid=WC0b01ac058004d5c1.
20. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/02/news_detail_002022.jsp&mid=WC0b01ac058004d5c1.
21. European Commission, http://ec.europa.eu/health/files/gmp/2014-02_pc_draft_gmp_annex.pdf.
22. European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/03/news_detail_002041.jsp&mid=WC0b01ac058004d5c1.
23. Dutch Medicines Evaluation Board, http://www.cbg-meb.nl/CBG/en/about/actueel/Hugo_Hurts_appointed_as_new_Director_Secretary_of_the_MEB/default.htm.
24. British Medicines and Healthcare products Regulatory Agency, http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON377633.
25. British Medicines and Healthcare products Regulatory Agency, http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON371778.
26. British Medicines and Healthcare products Regulatory Agency, http://www.mhra.gov.uk/NewsCentre/CON383422.
27. British Medicines and Healthcare products Regulatory Agency, http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesregulatorynews/CON383402.

28. British Medicines and Healthcare products Regulatory Agency, http://www.mhra.gov.uk/Howweregulate/Devices/Devicesregulatorynews/CON395239.
29. Health Canada, http://www.hc-sc.gc.ca/dhp-mps/compli-conform/info-prod/drugs-drogues/actingre-gui-0104-eng.php.
30. US Food and Drug Administration, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHVisionandMission/ucm384132.htm#top.
31. US Food and Drug Administration, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm386685.pdf .
32. US Food and Drug Administration, http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm274966.htm.
33. US Food and Drug Administration, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm386366.pdf.
34. Reuters, http://www.reuters.com/article/2014/02/21/us-usa-drugs-otc-idUSBREA1K1EW20140221.
35. US Food and Drug Administration, http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf.
36. US Food and Drug Administration, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm386275.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery.
37. US Food and Drug Administration, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ImportingandExportingDevices/ExportingMedicalDevices/default.htm.
38. US Food and Drug Administration, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf.
39. US Food and Drug Administration, http://blogs.fda.gov/fdavoice/index.php/2014/02/why-fda-supports-a-flexible-approach-to-drug-development/.
40. US Food and Drug Administration, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm388813.htm.
41. US Food and Drug Administration, http://blogs.fda.gov/fdavoice/index.php/2014/03/whats-new-in-the-fdas-2015-budget/.
42. US Food and Drug Administration, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389069.pdf.
43. US Food and Drug Administration, http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm390058.pdf.

ISPE Affiliates and Chapters: Local Connections. Global Impact.



Boost your knowledge. Expand your network.

ISPE's Affiliates and Chapters are your local resource for all things ISPE—from translations of ISPE's world-renowned Guidance Documents to education on regional industry and regulatory trends.

Get involved with your regional Affiliate or Chapter to meet industry leaders in your area, contribute your expertise to industry-advancing initiatives at the local level and share best practices with like-minded professionals.

ISPE

Connecting a World of Pharmaceutical Knowledge

Get Involved With Your Affiliate or Chapter Today!
ISPE.org/Affiliates-and-Chapters

HONORING INNOVATION

Facility of the Year Awards

2014 Category Winners

Category Winner – Equipment Innovation

Boehringer Ingelheim

Project: Aseptic Area 5 and Combi Line
Location: Biberach/Riß, Germany
Project Mission: to implement a modular concept for capacity expansion of a new facility for aseptic manufacturing of biopharmaceutical drug products.

Category Winner – Sustainability

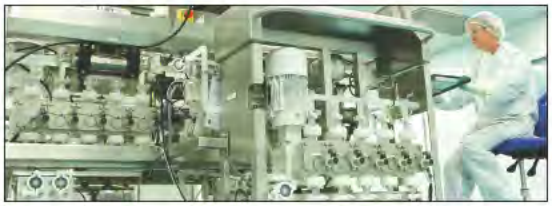
F. Hoffmann-La Roche Ltd.

Project: B250 – Q2K (Quality to Kaiseraugst)
Location: Kaiseraugst, Switzerland
Project Mission: to build a new laboratory building for quality assurance and quality control.

Category Winner – Project Execution

Grifols Therapeutics Inc.

Project: Grifols North Fractionation Facility (NFF)
Location: Clayton, North Carolina, US
Project Mission: to provide Grifols' critical care patients with a safe and reliable supply of life saving therapies.



Category Winner – Process Innovation

Patheon Pharma Services

Project: Biologics Plant of the Future
Location: Brisbane, Queensland, Australia
Project Mission: to design and construct a world-class, cGMP scale-up biopharmaceuticals manufacturing facility.

Category Winner – Facility Integration

Penn Pharmaceuticals Services Limited

Project: Penn Contained Manufacturing Facility (Penndragon)
Location: Tredegar, Gwent, United Kingdom
Project Mission: to create a multiple use API solid dose facility capable of handling batch sizes up to 120 kg for molecules with DELs down to 0.01 microgram/m.

Category Winner – Operational Excellence

Pfizer Ireland Pharmaceuticals

Project: NSI Capacity Expansion
Location: Dublin, Ireland
Project Mission: to increase manufacturing capacity for Prevenar® and Somavert®.

Honorable Mention – Process Innovation

WuXi Apptec Biopharmaceuticals Co., Ltd.

Project: Fully Single Use mAB Production Facility
Location: Wuxi City, China
Project Mission: to be the first biologics manufacturing facility in China using 100% single use technology and meet cGMP standards of the US, EU, and China.

www.FacilityoftheYear.org

FOYA – Celebrating 10 Years

ISPE's Facility of the Year Awards (FOYA) program is the premier global awards program recognizing innovation and creativity in the pharmaceutical and biotechnology manufacturing industries. Now in its 10th year, the FOYA program showcases accomplishments in facility design, construction and operation. It celebrates the shared commitment and dedication of individuals working for different companies worldwide to enhancing patient health and safety through innovation and advancements in pharmaceutical manufacturing technology.

FOYA – Honoring Innovation

Projects selected for these prestigious awards set the standard for pharmaceutical facilities of the future by demonstrating excellence in the following categories:

- Project Execution
- Facility Integration
- Equipment Innovation
- Sustainability
- Process Innovation
- Operational Excellence

FOYA at the CGMP Conference

Project Category Winners for 2014 will be honored at the **2014 Facility of the Year Awards Banquet** which will be held on 3 June 2014 at the Hilton Baltimore Holiday Ballroom in Baltimore, Maryland. It will be held in conjunction with **ISPE's FDA CGMP Conference.** During the conference, ISPE will feature a dedicated FOYA display area which will highlight the category winners using a graphic display and video presentation. The conference is an opportunity to learn and focus on quality metrics and quality compliance tools and techniques, many of which are exemplified by these winning FOYA projects.

FOYA at the Annual Meeting

The 2014 FOYA Overall Winner will be announced during the plenary session at the **2014 ISPE Annual Meeting** which will be held from 12 to 15 October 2014 at Caesar's Palace, in Las Vegas, Nevada. During the Annual Meeting, the FOYA program will be highlighted and the 2014 Category Winners and the 2014 Overall Winner will be honored; there will be an education track that offers insight from 2014 Category Winners on their winning projects.

FOYA at Pharma EXPO

FOYA award winners also will be formally recognized as part of the ISPE exhibit at the **2014 Pharma EXPO** which will be held 2 to 5 November 2014 at McCormick Place in Chicago, Illinois. This world class exhibition, sponsored by ISPE and PMMI, will include a conference which will be covering topics on the latest technological and regulatory trends, best practices and practical applications of science and technology throughout the entire pharmaceutical lifecycle.

FOYA – Recognizing Excellence

ISPE's Facility of the Year Awards Program puts the spotlight on Category Winners' innovative solutions to updating and replacing aging facilities and equipment as well as their implementation of the most up to date and state of the art approaches to quality metrics and quality compliance. Participation and attendance at these ISPE events will not only provide information and education, but will be a source of inspiration when seeing how they have been implemented by these world class industry leaders from large and small companies around the world.

ISPE Concept Paper: Improving Access for Patients with Unmet Medical Needs

by Mark Corbett, Senior Vice President, Clinigen Global Access Programs

Around the world, countless patients with a high degree of unmet medical need are in urgent need of new therapeutic alternatives. For many of these patients, access to new innovative medicines via the well-defined clinical trial process or through commercial channels is not an option. Consider these scenarios:

- The patient does not live in close proximity to a clinical trial site.
- The patient does not meet trial eligibility requirements.
- The patient was enrolled in a trial, the trial has ended, but availability of commercial supply is delayed.
- The patient lives in a country where a new drug is not or will never become commercially available.

For patients with an unmet medical need who require a new therapeutic option, the wait for approval and commercialization may simply be too long. In these situations, emotions often run high and drug developers can find themselves on the receiving end of intense pressure to grant access and yet may be unsure as to available routes.

Fortunately, regulatory mechanisms exist in many countries around the world that may enable patients in these situations to gain access to medicines that are in clinical development, are unlicensed in a specific market, but licensed elsewhere or are in the Marketing Authorization Application (MAA) process. Such mechanisms are referred to by a number of terms, including compassionate use, named patient use, expanded access. and early access, to name but a few.

A concept paper currently in development by an ISPE Task Team will describe these access programs, the regulations governing them, and best practices for designing and implementing as well as ensuring patient safety and minimizing risk. Topics to be covered include:

- Understanding the global regulatory landscape
- Defining the scope, patient eligibility criteria and program timing
- Engaging internal and external stakeholders
- Managing the drug supply
- Managing global logistics

Access programs described in the upcoming concept paper afford companies the opportunity to meet ethical obligations and can offer patients with an unmet medical need a potentially life-saving, life-enhancing or life-extending treatment option, ahead of commercial availability. In addition, such programs can be highly effective in helping foster positive relationships with key opinion leaders and treatment centers, as well as providing an opportunity to gather limited, yet valuable, information about the use of a drug in a wider population, as compared to a clinical trial.

Demand for access outside conventional clinical and commercial routes may come from patients and physicians anywhere in the world and is readily amplified via social media.

Patients can easily obtain information about drugs in development via the internet and are leveraging social media tools to appeal to companies from which they are seeking access and to call greater attention to their needs.

Rather than waiting for inbound requests from patients and healthcare providers, many companies proactively establish access programs as they anticipate demand for their drugs. Among the circumstances likely to stimulate demand are:

- Promising, well-publicized results from clinical trials

The concept paper on access programs represents a collaborative effort by a number of industry experts:

Elizabeth Cooper
Manager, Supply Chain Operations
Clovis

Mark Corbett
Senior Vice President
Clinigen Global Access Programs

Marie DeGayner Kuker
President
Kuker Regulatory Consulting

Delphine Fabry
Project Leader, Clinical Supplies
Sanofi

Rachel Huskisson
Regulatory Affairs Manager
Clinigen

Sheri Smith
President
Courante Oncology

Improving Access

Continued.

- Drugs offering a novel mechanism of action
- Drugs for diseases or conditions for which there are no or limited therapeutic options
- Conclusion of a successful clinical trial and the desire to maintain access to the drug for trial participants
- The gap between the New Drug Application (NDA) submission and approval
- Central approval via the European Medicines Agency (EMA), but delays in commercial availability and/or reimbursement in member states
- Commercial availability in one territory or region, but not available elsewhere
- Availability of a new therapeutic option for a rare disease with a patient population spread thinly around the world

In all of these scenarios, access programs can provide a route for patients to obtain innovative drugs prior to approval or launch, potentially helping those who have run out of therapeutic options.

Greater awareness of these programs and how they work is essential for all stakeholders. Similarly, an understanding of when these programs can and cannot be used (and why) is critical when the need presents itself. The upcoming concept paper will provide an overview of these access mechanisms and offer guidance to companies considering a program to help ensure success.

The concept paper will be available on the ISPE website this summer; availability will be announced via email containing a link for downloading.

GAMP Good Practice Guide – A Risk Based Approach to Regulated Mobile Applications

The development of mobile computing, especially increasing use of smartphones and tablets, has led to a major change in how computers are used. A large proportion of the population can now carry considerable computing power in such portable devices.

Given the availability of such computing power, it was inevitable that the life sciences industry would attempt to leverage it. In some cases this clearly leads to regulatory implications. Nobody would argue that the iPhone-based electrocardiograph approved by FDA in 2012 is not a medical device, and that it requires a wide variety of controls like any other sophisticated electronic medical device. However many mobile applications, or mobile apps, are created for other purposes, such as support for marketing. Regulators have recognized this increased use of mobile medical apps, as shown by FDA's publication of guidance on that topic in 2013.

The largely uncontrolled nature of the mobile platforms upon which such regulated apps must run present a challenge to companies wishing to use them. For traditional validated applications, one element of maintaining a state of control is controlling the platforms upon which they run. When the platform is a mobile phone used casually by members of the public the control of the platform becomes a significant challenge.

This guidance applies the GAMP® 5 approach to the uniquely challenging mobile environment. As such, it applies a risk management strategy intended to ensure that mobile medical apps, or mobile apps used in other GxP contexts, are validated, and can be delivered to customers as the safest and most effective possible solutions.

Practitioners wishing to apply this guide should have some basic understanding of the relevant Health Authority regulations. In the case of mobile medical apps, familiarity with the requirements of the medical device directives and regulations is especially valuable. In addition, basic knowledge of the classification of medical devices is important to understanding critical issues like what apps may require pre-market approval.

A particular challenge is that it can be difficult to distinguish between regulated and non-regulated apps. Sometimes despite the initial intent of the developer or the sponsor an app may turn out to be subject to regulations. This is can easily happen to apps that are developed to support marketing efforts, because the differences between a regulated and an unregulated application can be quite subtle. For example, FDA notes in their 2013 guidance on Mobile Medical Applications that a dosage calculator that considers only weight and gender is not a medical device, but if information related to disease state is entered (e.g. blood pressure, blood glucose levels, etc.), then the software would be regarded as a medical device.

Scope

This guidance covers the approach to validation and control of a variety of application types that run on mobile platforms. In this sense, the term "mobile platform" typically refers to smartphones and tablet computers. The vast majority of such systems will run on one of three operating systems: Apple iOS®, Google Android®,

Concludes on page 75.

ISPE and DIA Computer Systems Compliance Workshop

Maintaining Data Integrity and Reducing Patient Risk

The modernization of data collection and storage using computerized systems is progressing at a precipitous rate. New technology supporting products throughout their lifecycles are making global headlines. Recent awareness and recognition of the benefits and potential risks of computerized data are changing the regulatory approach in both Europe and the US.

Pharmaceutical stakeholders must be confident in data integrity implementations managed through their product's lifecycle. With technological innovations driving clinical and operational processes, manufacturers must be prepared to anticipate and mitigate problems in data integrity within each manufacturing phase. Such varieties in computer-system improvements must have multiple management systems based on today's business risk.

ISPE and DIA recognize the need for stakeholders to embrace the newest technology while retaining regulatory compliance and commitment to the patients they serve. On 6-7 November 2014 in Basel, Switzerland, both organizations will provide a forum for information and discussions on conceptual and practical data integrity methods. Experts in regulating computerized systems will share experiences through lectures, panel discussions, and interactive workshop sessions. These expansive sessions will focus on varied approaches piloted by two leading organizations within the life science sector. Each approach pursues the subject from diverse directions, but preserves the objective of ensuring data integrity and reducing patient risk. Forums will follow to discuss similarities of key principles and practices, in addition to the unique challenges associated with new technologies, such as cloud computing.

About DIA

DIA is the global connector in the life sciences product development process. The association has more than 18,000 members and builds relationships by bringing together regulators, innovators, and influences to exchange knowledge and collaborate in an impartial setting. DIA's network creates unparalleled opportunities for knowledge exchange with support from inter-disciplinary experience for the preparation of future developments.

DIA is an independent, non-profit organization headquartered in Washington, D.C., US with a European office in Basel, Switzerland, and additional offices in Horsham, Pennsylvania, US; Tokyo, Japan; Mumbai, India; and Beijing, China. For more information, visit www.diahome.org.

Computer System Compliance Program Committee, Basel, 2014

Representing ISPE:

Chris Clark, Head of Computerized Systems QA, Bard Pharmaceuticals Ltd, United Kingdom

Anders Brummerstedt, CPIP, Senior Project Manager, PEC A/S, Denmark

Representing DIA:

Rolf Banholzer, Global Head GxP IT Systems & Processes, Development QA, Novartis Pharma AG, Switzerland

Breffni Martin, Legal Representative, Optum Ireland

Key Topics

- Regulatory perspectives on data integrity and new technologies
- Relationship principals between GAMP®5 and clinical systems
- Business Process Risk Management
- Maintaining data integrity
- Industry challenges of emerging computing strategies (mobile and cloud-based)

ISPE and DIA's computer systems compliance workshop is aimed at intermediate and experienced professionals interested in gaining an awareness of the principles of GAMP® 5 risk-based approaches to compliant GxP computerized systems and data integrity maintenance support. Contract Research Organizations (CROs), including those from regulatory affairs, quality assurance stakeholders, and Computer System Validation (CSV) practitioners will find forums focused on understanding regulatory concerns, identifying key challenges, and a perspective exchange on the anticipated opportunities and risks arising from newly applied technology. Technology service providers will find substantial knowledge within pharmaceutical data discussions on the development of principals and practical solutions needed to meet the challenges of data integrity throughout each phase of a manufactured pharmaceutical product.

Within the modernization of today's pharmaceutical

Maintaining Data...

Continued.

manufacturing process, data integrity is significant to reducing risk for global health and safety. ISPE continues its commitment to the advancement and technical efficiency of its members and is joined by DIA to provide a current and applicable workshop in Basel, a region well-known for its unique concentration of innovative pharmaceutical companies, research institutes, and universities. As the center of Swiss life-sciences, "BioValley" is anticipated to be a premier workshop site, attracting pharmaceutical professionals from around the world. For more information on the Basel workshop on 6-7 November 2014, "Maintain Data Integrity to Reduce Risk for the Patient," visit www.ISPE.org or email ask@ISPE.org.

GAMP Mobile Apps

Continued from page 73.

and Microsoft Windows® (phone, RT®, or tablet/PC variations), but mobile platforms using other operating systems are also in scope.. While all smartphones are capable of communication via cellular radio, tablet devices may or may not have that capability. All mobile devices, however, do at least have WLAN (Wireless Local Area Network) connectivity.

This guidance does not focus on the mobile devices themselves, although it does acknowledge and make address their importance. Unlike traditional infrastructure, it may be very difficult for a regulated company to exert control over the hardware/OS platforms, mainly because they may be the property of individuals and not corporate capital assets. As a result the guide focuses on software development and software and procedural controls.

This guide is not intended to cover all aspects of medical device registration, development, and support, but rather to show how current industry good practice as described in GAMP guidance may be applied to mobile apps.

While this guidance presents approaches to controlling non-regulated mobile applications, some of the controls and considerations are unique to medical devices and may introduce constraints that are not necessary for such applications. Practitioners need to understand the risks to public health related to their apps.

For additional information on other ISPE GAMP Guides, http://www.ispe.org/gamp-good-practice-guides.

Did You Know? You Can Try ISPE's Expanded eLearning for Free

Recently, ISPE launched several expanded eLearning courses, including Auditing for the Pharmaceutical Industry, Basic Principles of Computerized Systems Compliance (GAMP® 5), Biotechnology and Containment Fundamentals. Now, with the introduction of free interactive demos for each of the courses, you can sample the course content and familiarize yourself with the mechanics of taking the courses before enrolling, so you can determine if eLearning is right for you. For a more in-depth trial of ISPE's eLearning offerings, the complete first module of the Auditing course is available free of charge at **www.ISPE.org/Expanded-Online-Training-Courses**. Other things you may not know about ISPE's eLearning offerings:

- Our eLearning products have been developed to meet the unique needs of pharmaceutical manufacturers, service providers and industry leaders
- Our eLearning products are in use in more than 76 countries
- 90% of eLearning purchasers have purchased more than one course
- We offer more than 150 products in 22 topics
- 98% of users stated that they would recommend an eLearning course to their colleagues

Each course offers a pre- and post-assessment to measure your learning, narrated course content with engaging graphics and exercises, a downloadable course presentation for note-taking and links to regulatory and industry information. ISPE's new eLearning courses are intended to help you get the training you need in a manner that is convenient to you, on your schedule and at your pace. ISPE's eLearning courses also eliminate travel time and costs, making them an economical way to meet annual training requirements.

The interactive demos are available to try at www.ISPE.org/eLearning.

ISPE Classroom Training 2014

Step up your Knowledge in Barcelona

Learn how to improve manufacturing efficiency, maintain product quality, and improve GMP compliance.

Barcelona, Spain will host industry leaders as they present training courses with the unparalleled quality you expect from ISPE. Courses have been designed to delve deeply into specific topics and provide knowledge and skills using lecture, breakouts, and applicable exercises. Tangible take-aways will provide immediate opportunities for application of objectives and trade knowledge increasing your professional role in the pharmaceutical industry.

Expert instructors have been drawn from ISPE members from around the world to assure the highest degree of information in technological advancements, approaches to regulatory compliance, and practical industry solutions. ISPE guidance documents supplement most courses, providing practical, real world information to reinforce and update industry best practices and support your fundamental base on the next level.

ISPE CEUs are awarded four weeks after the event and are based upon verification of attendance and receipt of a completed course evaluation. Some courses include a pre-recorded course primer. Access information will be provided via email one week prior to the start of the training event.

ISPE has been reviewed and approved as a provider of project management training by the Project Management Institute (PMI®).

Monday, 8 September 2014

A Risk-Based Approach to GxP Process Control Systems: Applying the GAMP Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (2nd Edition) (T21)

Course Level: Intermediate

Instructors: Hilary Mills-Baker, Director, Rhombus Engineering Ltd. and Karen Ashworth, Director, Karen Ashworth Consulting

CEUs: 1.5 **COP:** GAMP

Who Should Attend:

Quality assurance and quality control specialists, validation specialists, manufacturing supervisors, technical support personnel, engineers, MIS professionals and all levels of management who need a fundamental understanding of computerized system compliance and computer system vendors or consultants, engineering contractors, and validation service companies.

Course Description:

Are your process control systems fit for use?

This highly interactive course recommends good practices based on a lifecycle approach for the development and management of process control systems. Practical applications of the principles and concepts of GAMP® 5 will be discussed in regard to process control systems. The course also covers both regulated company and supplier quality management systems and the full system lifecycle from concept to retirement. Participants will learn the integral parts of the normal system lifecycle, such as QRM and specification/verification activities. The course also promotes leveraging of supplier documentation and methods to avoid unnecessary duplication, cost, and waste.

Immediately apply the course objectives using the complimentary copy of the *GAMP® Good Practice Guide: A Risk-Based Approach to GxP Process Control Systems (Second Edition).*

Additional Offerings:

This course is also offered at the Tampa, FL training event on 1-2 December.

Facility Project Management in the Regulated Pharmaceutical Industry (T26) – UPDATED COURSE!

Course Level: Intermediate

Instructor: Patricia M. Melton, BSC, MBA, PhD, Managing Director, MIME Solutions Ltd.

CEUs: 1.3 **PMI PDUs:** 13 **COP:** Project Management

ISPE has been reviewed and approved as a provider of project management training by the Project Management Institute (PMI®).

This course includes content from a Guide to the Project Management Body of Knowledge (PMBOK Guide®), Fifth Edition. Copyright 2013 Project Management Institute (PMI®).

Visit ISPE's website and register under Fees and Registration: www.ISPE.org/2014-barcelona-training

Step up your Knowledge in Barcelona

Continued.

Who Should Attend:
Personnel entering facility project management coming from another discipline within the pharmaceutical industry; those with 2-3 years of experience within a project role looking to improve their project delivery capability; engineers, project engineers, quality and IT professionals likely to support or deliver projects within their role, and managers who are likely to sponsor projects.

Prerequisite:
Attendees should have an understanding of GMP and the pharmaceutical industry as well as the basic concepts of project delivery (i.e., cost, schedule and scope planning and control) prior to attending the course.

Course Description:
Do you have the tools for successful project delivery?
This interactive course provides comprehensive project basics and develops the concept of project lifecycle from initiation through delivery, as well as tools to manage all project resources. The course focus is targeted to facility project needs within the regulated pharmaceutical industry and establishes the innate value inherent of "good practice" project management. Each course module introduces key project management concepts, tools, and methodologies that specifically support successful project delivery.

Immediately apply the course objectives using a complimentary copy of the ISPE Good Practice Guide: Project Management for the Pharmaceutical Industry.

Additional Offerings:
This course is also offered at the Raleigh, NC training event on 19-20 November.

Science and Risk-based Commissioning and Qualification - Management for Commissioning and Qualification (T40)

Applying the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification

Course Level: Intermediate
Instructor: Lynn Bryan, Qualified Person, Ballygan Consulting
CEUs: 1.5 **COP:** Commissioning and Qualification

Who Should Attend:
Intermediate practitioners of commissioning and qualification who want to understand and use the science- and risk-based approach. Project engineers and managers, commissioning and validation professionals, engineering service providers, quality assurance personnel involved in qualification, validation and regulatory.

Course Description:
Is your equipment and facility "fit for use" as defined by current global regulatory authorities?
Through interactive workshops, this course will help you explain and apply the science- and risk-based approach to verification of systems, equipment, and facilities in accordance with the ICH documents Q8(R2), Q9, Q10 and ASTM E2500. Topics covered include the principles and activities that constitute an efficient and acceptable approach to demonstrating facility and equipment fitness for use as required by major global regulatory authorities; improving the ability to meet documented process requirements; controlling risks within the manufacturing process, and producing high quality products and consistent operation to meet product user requirements. Guidance on the transition of an organization's approach to commissioning and qualification to one that incorporates a science- and risk-based approach will be discussed.

Immediately apply the course objectives using a complimentary copy of the new ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification.

Applying Quality Risk Management (T42)

Course Level: Intermediate
Instructor: Alice Redmond, PhD, Vice President, Commissioning Agents, Inc.
CEUs: 1.5 **COP:** Commissioning and Qualification

Who Should Attend:
This course will be of interest to project engineers, project managers, commissioning and validation professionals, engineering service providers, and quality assurance personnel involved in qualification and validation and regulatory.

Prerequisite:
It is strongly recommended that participants should be familiar with basic concepts of ICH Q8(R2), Q9 and Q10 and a fundamental understanding of risk-based C&Q prior to attending this course. The course will not focus on the detail of the tools, but the overall risk management process. However, working examples of different tools will be given to enhance learning and understanding.

Course Description:
Do you have the tools to manage risk?
Through interactive workshops, this course will explain and apply the key principles of QRM programs that need to include Quality System elements (ICH Q10) within the product/system lifecycle. Discussion topics include: the philosophy and application of a holistic QRM process through

Step up your Knowledge in Barcelona

Continued from page 77.

a QRM plan; developing and implementing a risk decision tree; appropriate use of risk assessment tools; applying risk management methodologies throughout design and verification phases; format and maintenance of a risk dashboard; and practical summarizations of US/EU/FDA/ and WHO regulatory expectations influencing the implementation of a holistic QRM process.

Immediately apply the course objectives using the complimentary copy of the *ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification* and the ICH Q8(R2), Q9 and Q10 mini-regulation handbooks.

Additional Offerings:
This course is also offered at the Tampa, FL training event on 1-2 December.

Tuesday, 9 September 2014

Practical Application of Technology Transfer – New Course and Guide!

Course Level: Intermediate
Instructor: Bruce Davis, Principal, Global Consulting
CEUs: 1.3 **COP:** Product and Process Development

Who Should Attend:
This course is intended for professionals involved in technology transfer in relation to commercial transfer between manufacturing sites and transfer to manufacturing from or within development. Professionals with technology transfer responsibilities including regulatory compliance associates, process development scientists, facilities engineers, validation and quality assurance specialists, manufacturing managers, and regulators.

Course Description:
Does your technology transfer reflect an enhanced approach to current best practices?
This course focuses on technology transfer including knowledge transfer and science, risk-based principles (ICH Q8R2, Q9, Q10, Q11). Through better process understanding, this course identifies critical items for success and provides 'how to' examples which can be individually tailored, depending on the type and scope of transfer. The course uses the ISPE Good Practice Guide: Technology Transfer (Second Edition), developed with industry experts, and utilizes current industry challenges and real-world examples as tools for industry and regulators to use when conducting and evaluating technology transfer activities.

Immediately apply the course learning objectives using the complimentary copy of the *ISPE Good Practice Guide: Technology Transfer (Second Edition).*

Additional Offerings:
This course is also offered at the ISPE Annual Meeting event on 14-15 October.

Sterile Product Manufacturing Facilities: Applying the ISPE Baseline® Guide and FDA Guidance Principles to Design and Operation (T12)

Course Level: Intermediate
Instructor: Gordon Farquharson, Managing Director, Critical Systems Ltd.
CEUs: 1.3 **COP:** Sterile Products Processing

Who Should Attend:
Engineers, validation scientists, quality assurance specialists, and manufacturing managers. Professionals who want a fundamental understanding of sterile manufacturing facilities and their design, renovation, and operation. Engineering firm professionals and other consultants who work with the pharmaceutical industry.

Prerequisites:
Participants interested in commissioning and qualification should attend the Science and Risk-based Commissioning and Qualification – Applying the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification training course.

Course Description:
Do you know the key requirements and GMPs for sterile manufacturing facilities?
This course uses the second edition of the ISPE Baseline® Guide: Sterile Product Manufacturing
Facilities and the FDA's Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice to provide an understanding of the key requirements and GMPs for sterile manufacturing facilities. Using the referenced documents, this course will cover regulatory philosophy, aseptic process and equipment considerations, aseptic clean room design and operation, differential pressure requirements, airlocks, basic utility systems, European HVAC considerations, basic commissioning and qualification issues, and a brief introduction to barrier isolation technology.

Immediately apply the objectives using a complimentary copy of the *ISPE Baseline® Guide: Sterile Product Manufacturing Facilities (Second Edition).*

Additional Offering:
This course is also offered at the Atlanta, GA Training Event on 9-12 June.

ISPE Investigational Products European Conference

17 – 18 September 2014
Barcelona, Spain*

NEW STRATEGIES
to improve clinical supply chain performance.

BEST PRACTICES
to balance multiple regulatory requirements.

INNOVATIVE PROCESSES
to decrease cost/time for clinical supply delivery.

*Brought to you by the Investigational Products European Community of Practice

www.ISPE.org/2014-InvestigationalProductsConference

Architects, Engineers, Constructors

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

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

NNE Pharmaplan, Nybrovej 80, 2820 Gentofte, Denmark. +45 4444 7777. See our ad in this issue.

Pharmadule Morimatsu AB, DanvikCenter 28, SE – 13130 Nacka, Sweden. +46 (0)8 587 42 000. See our ad in this issue.

Cleanroom Products

Azbil Telstar Projects S.A., 1504 Grundy's Lane, Bristol, PA 19007 (215) 826-0770. See our ad in this issue.

Consulting

NNE Pharmaplan, Nybrovej 80, 2820 Gentofte, Denmark. +45 4444 7777. See our ad in this issue.

PharmEng Technology, 2501 Blue Ridge Road, Suite 250, Raleigh, NC 27607. (416) 385-3922. See our ad in this issue.

Dust Collection Systems and Equipment

Camfil Air Pollution Control, 3505 S. Airport Dr., Jonesboro, AR 72401. (870) 933-8048. See our ad in this issue.

Electric Dry Steam Generators

Electropolishing

UltraClean Electropolish, Inc., 1814 Sunny Dr., Houston, TX 77093. (877) 823-7911. See our ad in this issue.

Facilities Design

Dagard, Route Du Stade, Boussac, France 23600. +33 555824027. See our ad in this issue.

HVAC – Filtration

AAF International, 9920 Corporate Campus Dr., Ste. 2200, Louisville, KY 40223. (502) 637-0320. See our ad in this issue.

Information Technology

COPA-DATA GmbH, Karolingerstrasse 7b, Salzburg, Austria 5020. +43 662 43 10 02-0. See our ad in this issue.

Instrumentation

Bürkert Fluid Control Systems, Christian-Bürkert-Strasse 13-17, D-74653 Ingelfingen, Germany. +49 (0)7940 10 0. See our ad in this issue.

Packaging Equipment

IMA S.p.A, Via Emilia, 428-442, 40064 Ozzano Dell'Emilia, Bologna, Italy. +39-051 6514 186. See our ad in the issue.

Process Engineering

Sturtevant, Inc., 348 Circuit St., Hanover, MA 02339. (781) 829-6501. See our ad in this issue.

Process Measurements and Control Systems

Finesse Solutions, 3501 Leonard Ct., Santa Clara, CA 95054. (408) 570-9000. See our ad in this issue.

Pumps

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

Fristam Pumps USA, 2410 Parview Rd., Middleton, WI 53562. (800) 841-5001. See our ad in this issue.

LEWA-Nikkiso America, 132 Hopping Brook Road, Holliston, MA 01746. (508)893-3218. See our ad in this issue.

Software Simulation and Processing Systems

Intelligen, Inc., 2326 Morse Ave., Scotch Plains, NJ 07076. (908) 654-0088. See our ad in this issue.

Validation Services

Azzur Group, LLC, 726 Fitzwatertown Rd., Ste. 6, Willow Grove, PA 19090. (215) 322-8322. See our ad in this issue.

Commissioning Agents, Inc., 652 N. Girls School Rd., Indianapolis, IN 46214. (317) 271-6082. See our ad in this issue.

ProPharma Group, Inc., 10975 Benson Drive., Ste. 330, Corporate Woods Bldg. 12, Overland Park, KS 66210. (913) 661-1662. See our ad in the issue.

Valves/Fittings/Hoses/Tubing

AGRU Kunststofftechnik GmbH, Ing.-Pesendorfer-Strasse 31, A-4540 Bad Hall, Austria. +43 7258 790. See our ad in this issue.

Gemu Gebr. Mueller Apparatebau Gmbh & Co. Kg, Fritz Mueller Str 6-8, D-74653 Ingelfingen-Criesbach, +49 (0) 79 40 123 708. See our ad in this issue.

Concludes on page 81.

Water Treatment and Purification

ELETTRACQUA Srl, Via Adamoli 513, 16165 Genoa, Italy. +39 010 8300014. See our ad in this issue.

Mar Cor Purification, 160 Stedman Street, Lowell, MA 01851. (978) 453-9600. See our ad in this issue.

Call for Articles

Pharmaceutical Engineering, ISPE's technical magazine, is looking for subject matter experts in the global pharmaceutical industry with knowledge of the latest scientific and technical developments, regulatory initiatives, and innovative solutions to real life problems and challenges who can contribute application articles and case studies.

Special features and guest editorials will be considered that focus on new technology, contemporary quality management practices, and production innovation.

New Departments include: facilities and equipment, information systems, product development, production systems, quality systems, research and development, supply chain management, and regulatory compliance.

Industry Hot Topics
In addition to the Departments, each issue of *Pharmaceutical Engineering* will feature industry relevant hot topics, including biosimilars, breakthrough therapies, next generation manufacturing, quality metrics, quality risk management, supply chain integrity, and sustainability.

November/December
Risk Management Strategies when Outsourcing Manufacturing
Article deadline: 9 July 2014 Magazine publishes: 24 November 2014

For more information, please visit www.pharmaceuticalengineering.org and click on "Submit Article."

PHARMACEUTICAL ENGINEERING® THE OFFICIAL TECHNICAL MAGAZINE OF ISPE

advertiser's index

ISPE Classroom Training

There's still time to register...

Improve product quality and increase process understanding with ISPE in-depth training courses

New and Updated Courses and Guidance Documents!

9 - 12 June 2014
Atlanta, GA USA

- Basic GAMP® 5 (T45)
- C&Q (T40)
- Combination Products (T47) - New Course!
- OSD (T10)
- QbD (T43)
- Sterile (T12)
- Technology Transfer (T19) – New Course and Guide!

8 - 10 September 2014
Barcelona, Spain

- C&Q
- GAMP® 5 Process Control Systems
- Project Management – Updated!*
- QRM – Updated!
- Sterile
- Technology Transfer – New Course and Guide!

8 - 11 September 2014
Philadelphia, PA USA

- Biopharmaceutical Manufacturing Processes
- Cleaning Validation - Updated Course Includes New Guide!
- Facilities Systems and Equipment Workshop – New Course!
- HVAC - New Course!
- Pharmaceutical Water Generation - Updated Course Includes New Guide!
- Process Validation in Biotechnology
- Storage, Delivery & Qualification of Pharmaceutical Waters – Updated Course Includes New Guide!

6 - 8 October 2014
Kansas City, MO, USA

- Basic GAMP® 5, Part 11 and Annex 11

14 - 15 October 2014
Las Vegas, NV, USA
ISPE Annual Meeting

- Technology Transfer – New Course and Guide!

17 - 20 November 2014
Raleigh, NC USA

- Clinical Trial Materials
- GAMP® 5
- HVAC - New Course!
- Pharmaceutical Water Generation - Updated Course Includes New Guide!
- Process Validation in Biotechnology Manufacturing
- Project Management – Updated!*
- Storage, Delivery & Qualification of Pharmaceutical Waters – Updated Course Includes New Guide!

1 - 4 December 2014
Tampa, FL

- Auditing
- Cleaning Validation – Updated Course Includes New Guide
- GAMP® 5 Process Control Systems
- Managing the Risk of Cross Contamination (Risk MaPP)
- Process Validation – New Course!
- Q7A
- QRM

Register early and save!

ISPE.org/Training

* ISPE has been reviewed and approved as a provider of project management training by the Project Management Institute (PMI®)

PINNACLE PROGRAMME 2014 GLOBAL SPONSORS

CAI | Azzur Group LLC | nne pharmaplan® Engineering for a healthier world

Expect more

– from heating and cooling for the pharmaceutical industry

Finding true quality and value means looking beneath the surface. Our tubular heat exchangers and point of use cooler for the pharmaceutical industry have all the features and innovations that make world-class equipment. What's more, they're backed by an unmatched level of service and support to secure lifetime performance. The bottom line: maximum uptime with minimum cost of ownership. With the broadest range in the industry, Alfa Laval can always supply the right heat exchanger for your task.

Scan QR code and learn more.
alfalaval.com/biopharm

ALFA LAVAL