PHARMACEUTICAL ENGINEERING®

THE OFFICIAL TECHNICAL MAGAZINE OF ISPE

SEPTEMBER/OCTOBER 2013 VOLUME 33, NUMBER 5

Sustainability

Energy Benchmarking

Construction Waste Reduction

Total Particulate Monitoring

Green Manufacturing

Dechlorination Methods

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See page 108 for a message from ISPE Annual Meeting Chairman Bob Chew.

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table of contents

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SEPTEMBER/OCTOBER 2013
VOLUME 33, NUMBER 5

supply chain management

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This issue of *Pharmaceutical Engineering* highlights topics that are at the ethical heart of the pharmaceutical industry: the protection of the public as well as the protection of the environment.

Sustainability has been identified as a goal for regulators worldwide. The UK Medicines and Healthcare products Regulatory Agency (MHRA), for example, have an action plan that includes measurable targets, and encourages best practice among staff, as well as ensuring that sustainability is an integral part of their procurement processes. They have committed to minimize waste and conserve energy and other natural resources by reducing, reusing, and recycling.

Typically, a pharmaceutical company will generate significant paper waste during the labeling process. Buker, et al, presents a timely update of an article, which shows how electronic management of labeling generates less waste due to fewer printed document. With the increasing importance of LEED and energy performance benchmarking, Capparella describes how to drive meaningful results into a building a successful energy management program and Wander compares several international building assessment systems and emissions reporting practices that could help global pharmaceutical companies develop sustainability policy. Bowen makes the case that there is a viable path to achieve sustainability that is particularly relevant to the pharmaceutical industry and the healthcare framework, focused on maintaining and improving the health of the patient. Cochran presents a successful example of building demolition waste reduction, focusing on the strategies and outcomes of implementing a plan to divert waste from the landfill and back into the supply chain during construction.

Regarding the protection of the public, in a recent statement to the Subcommittee on Health Committee on Energy and Commerce of the U.S. House of Representatives, Janet Woodcock, M.D. Director, Center for Drug Evaluation and Research, discussed securing the supply chain for prescription drug products. Regulatory efforts to secure the supply chain include minimizing risks that arise anywhere along the supply chain, from sourcing a product's ingredients through the overseeing of a product's manufacture.

Current challenges in GMP compliance and developments in supply chain integrity of active pharmaceutical ingredients are reviewed by Chan, et al, and several recommendations, including greater collaboration and harmonization of API regulations are discussed.

Other topics covered related to safeguarding the quality of the product and the safety of the patient, include implementation of Near Infrared Spectroscopy (NIRS) in Process Analytical Technology (PAT) by Fowler, choosing the optimal hygienic seal for process performance by Vogel, and alternative de-chlorination methods in reverse osmosis applications by Wilf. Best practices in total particulate monitoring in cleanrooms, RABs and isolators are described in an article jointly authored by the HVAC and Sustainability COPs.

In a guest editorial, Wilkins discusses managing the risk of cross-contamination when products are produced on sites that manufacture multiple products, including more than one class of the beta lactams, and the industry's adoption of Risk-MaPP to ensure risk is being managed to acceptable levels.

This issue also features an exclusive interview with Julie Kim, Global Franchise Head of Biotherapeutics, Baxter International, Inc. who discusses Baxter's expanding capacity around the globe to address plasma-derived therapies and her role in bringing a state-of-the-art manufacturing facility to Covington, Georgia. In addition to the technical lineup, there are articles on several ISPE initiatives, including the drug shortage survey, breakthrough therapies, and the Annual Meeting.

Finally, the digital edition and PE Web site will feature an online exclusive article by Potter, et al, summarizing the rationale, objectives and challenges for ISPE's Quality Metrics project, which is a response by industry to FDA initiatives to help move the pharmaceutical industry toward the 'desired state' and to help address the problem of drug shortages.

I hope you find this issue of *Pharmaceutical Engineering* informative as well as thought provoking. I welcome your feedback – email me at ghall@ispe.org.

Gloria Hall
Editor, *Pharmaceutical Engineering*

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Industry Relies On ISPE and We Are Delivering

ISPE President and CEO highlights the technical programs and leadership initiatives underway as ISPE continues its focus on important manufacturing, technical, quality and regulatory issues to help members become more knowledgeable.

Late last year, I wrote about ISPE's plans to become even more relevant by better understanding the challenges facing Members and their companies and responding with more appropriately positioned programs and services. We know that you rely on ISPE for relevant technical leadership--for information on hot topics, education and training, publications and valuable networking opportunities. I am happy to report that ISPE is delivering on our transformational promise through a multitude of new technical programs and leadership initiatives.

True to the Society's mission, we continue to focus on important manufacturing, technical, quality and regulatory issues to help Members become even more knowledgeable. A few of the more visible activities underway include new work groups producing technical articles and documents and other new projects focused on hot topics—issues that are on the minds of Members, regulators and company leaders like drug shortages, quality metrics, innovations in manufacturing, operational excellence and the production implications associated with breakthrough therapy approvals, just to name a few.

Our Product Quality Lifecycle Implementation (PQLI) is leading industry's Quality Metrics Initiative with support of the International Leadership Forum (ILF) and regulators. The first Quality Metrics Workshop took place at the annual ISPE-FDA CGMP Conference in June (Baltimore, MD USA) with "filled to capacity" discussions. The Work Groups supporting this Initiative produced a discussion paper summarizing the June Workshop while also planning a second Workshop to be held during ISPE's Annual Meeting (3-6 November, Washington, DC, USA).

Since the ISPE Drug Shortages Survey Report was released in June, the US FDA referenced ISPE's survey in their drug shortages report to the United States Congress; the survey was covered in the *Wall Street Journal Online* and 375 other news sources and ISPE presented the survey findings to EMA, MHRA, other societies, regulators and patient groups. Visibility generated from the survey reflects positively on ISPE's technical leadership – follow-up to this study is underway.

ISPE's relationships with global regulators are important in helping the Society produce valuable technical and regulatory information. Our Regulator Members appreciate being a part of ISPE's networks and they value the important role ISPE serves as a convener of discussions. As an individual Member Society, ISPE offers Regulators access to an expert network of 20,000 unbiased scientists, engineers and leaders. Industry *and* regulators rely on ISPE.

Technical leadership is just one theme running throughout ISPE's 2013 Annual Meeting. This year's Annual Meeting is shaping up to be an extraordinary event and potentially the largest event in Society history. In addition to 275 speakers presenting case studies on manufacturing, quality, investigational products, information systems, facilities and other traditional ISPE topics, this event includes first-ever discussions and reports on ISPE Industry initiatives including Quality Metrics, Breakthrough Therapies and Drug Shortages; special sessions on Quality by Design (QbD), Today's Global Supply Chain (in collaboration with Rx360), a Workshop featuring BU/CU discussions, a session on Operational Excellence, a Global Regulatory Summit and much more. This meeting reflects ISPE's transformation—a new look and evidence of technology leadership that industry can rely on.

For more information and to register, check out additional information at www.ispe.org/2013-annual-meeting.

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Labeling Pharma "Green" and Compliant in a Track and Trace World

by Dana Buker, David Loy, and Harini Pillalamarri

This update presents a discussion of the current regulatory landscape and how compliance and a "green" approach can merge for the benefit of suppliers, regulatory bodies, and the general public as well. The original article introduced arguments for the implementation of an electronic labeling system in the life science industries with a focus on the sustainable "green" benefits of electronic label management.[1]

The electronic management of product labeling; including the design, review, approval, transmission, printing, tracking, and reconciliation of labels is becoming more prolific in the life sciences because of the inherent control, efficiency, and accuracy benefits. However, today we are facing additional pressure to implement this technology based on new regulations to meet e-pedigree/track and trace requirements for pharmaceuticals and Unique Device Identification (UDI) for medical devices. Not only are the software, middleware, and internet infrastructure products ready to meet the challenge, but so too is the hardware including high-quality, high-speed, high resolution color, and other specialty in-line printers. That is, with the exception of integration to the to-ne databases that will hold the supply chain data.

This article will describe and discuss the more impactful considerations of electronic labeling systems from an internal business perspective as well as from an outward-facing regulatory perspective.

Sustainable manufacturing issues have come to the forefront of recent news with the concept of "green" driving many new initiatives. In life sciences manufacturing, there are many processes that produce large amounts of waste, expend excess energy, increase costs, are inefficient, and can introduce a greater level of risk than necessary. While many processes can become more environmentally responsible and economical, one process that could be improved with relatively low implementation overhead is the design, approval, control, printing, and application of product labels. Moreover, regulations such as FDA's Unique Device Identification and the pending "California Rule" for e-Pedigree introduce the need for electronic transmission of data as product enters or re-enters the supply chain. Although these regulations may be thought of more in terms of their benefit to public safety, one also can easily argue that they are by their nature (no pun intended) inherently "green" because they are dependent on electronic rather than manual hard-copy systems.

Since many life science manufacturers and distributors need to comply with existing and soon-to-be regulations, it is an optimum time (or perhaps a bit overdue) to consider the systems available today that can deliver efficiency and compliance to labeling processes. It may be time to re-evaluate the need for upgrading processes such as pre-printing, holding, releasing, moving, and re-releasing labeling materials at packaging time. Today, it is possible to perform most of that work electronically so that the packaging operation includes merging variable data (including serial numbers and/or UDI numbers) onto, more or less, blank label stock in real-time.

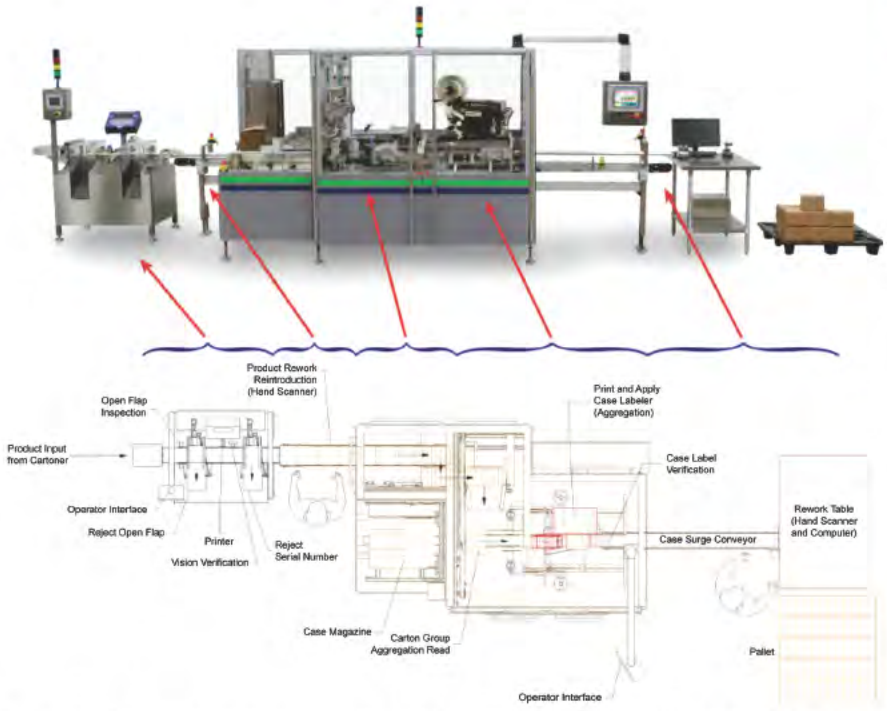

Figure 1. High-speed packaging line with in-line printer and operator/station interface legend.

What is an Electronic Label Management System and What Makes it "Green"

In a simplified view, an Electronic Label Management System (ELMS) can be thought of as providing infrastructure to support three primary tasks: Label Design, Label Approval, and Label Printing. Below is a brief description of each:

1. **Label Design:** when there is a validated ELMS in place, the design process takes place in a controlled environment that tracks the label version, effectivity, creation date, operator, and other important Meta data in a secure database. Once a label design draft is completed, the approval process can send the template image as an attachment through a workflow simultaneously to all reviewers as seen in Figure 2.

2. **Label Approval:** the system architecture can allow for a global approval

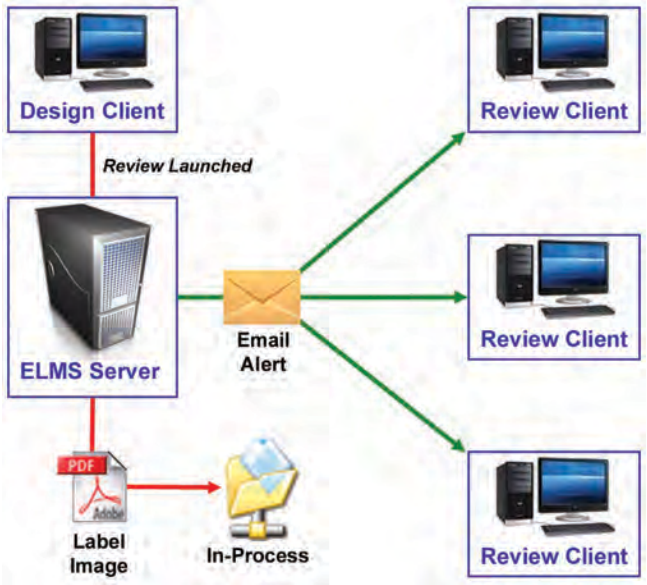

Figure 2. Label Design. New or updated label review notification process via email using an Electronic Label Management System (ELMS).

process. In this case, the company's Wide Area Network (WAN) is used to facilitate communication among the reviewers who can share comments and document feedback electronically in real-time in order to dramatically improve the overall label template approval process as seen in Figure 3.

3. **Label Printing:** once the approval workflow is complete, the label template version is approved with its effective begin and end dates. The template may then be assigned to product(s) lot(s) at packaging time. The approved label image is then ready to accept variable lot and serialization data. The ELMS will have been interfaced with a validated ERP, MES, PLM, and/or other database(s) so that the variable data are available for merging into the template at print time. Labels are printed on demand and applied to individual containers, cartons, shippers, bundles, and pallets during final packaging for a fully automated print-and-apply process. The need for pre-printing and all of the related costs, lead times, and controls will have been eliminated as seen in Figure 4.

The use of browser-based applications for label production is highly resourceful and efficient. The application will be readily available from any workstation that has access to the network. Browser-based applications also can be made available externally, eliminating the need for exporting data to a vendor for printing labels, and avoiding the risk of data loss during the transfer of information from one location to another. The required safeguards to protect a browser-based system is facilitated by using stringent login credentials and appropriate validation. All global packaging operations including outsourced vendors can be assured of printing the most recent approved version of label(s).

What are the Benefits and Risks of an ELMS?

The benefits of an ELMS include, but are not limited to:

Speed and Efficiency

- Inventory: electronic systems require no inventory (except

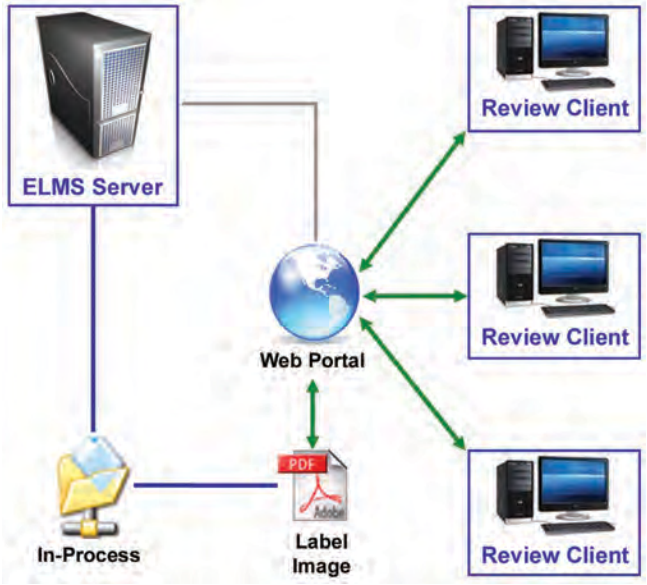

Figure 3. Label Review and Approval. New or updated label design review via the internet in an Electronic Label Management System (ELMS).

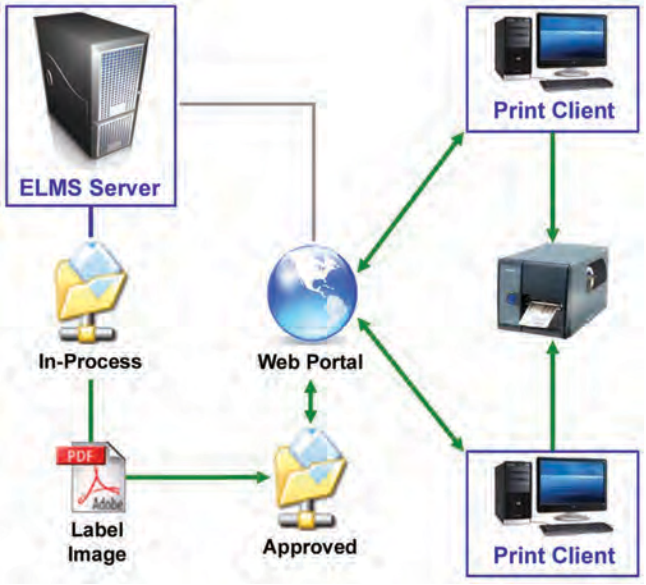

Figure 4. Label Printing. Label printing using an Electronic Label Management System (ELMS).

unprinted or partially printed label stock), so there is a dramatic reduction in inventory and related management and control costs.
- Planning Resources: planning and scheduling is improved since no inventory means no need to plan and schedule.
- Material handling: material handling is dramatically reduced since there is no need to move pre-printed labels from storage to the packaging area at packaging time.
- Quality Resources: QA review is improved since the use of validated systems precludes the need for active approval of labels at packaging time.
- Standard Label Approval: the linear approval process inefficiencies are eliminated. In the linear hard copy flow, the label was designed and printed, it was then sent around to the necessary departments for review and approval. On average, four to five employees were part of the label approval process and the movement of the paperwork from one to the next required that the prior person's approval be given before the file was sent to the next person. By contrast, when using an ELMS different departments work concurrently rather than in an ordered line, employees are more efficient and the elapsed time to complete the routing process can be significantly reduced. An electronic review and approval process not only reduces paper and office supply costs by omitting the need for paper and hard copy files, but it also simplifies and speeds up the process while reducing the chance of errors and omissions.
- Expedited Approval: perhaps the most obvious improvement from the ELMS is the ability to address rush items. With a 100% electronic web-enabled system, expedited items can get through the entire routing and approval system within hours due to the ability to access the system from anywhere at any time. This elevated efficiency can reduce costs since the use of couriers or other relatively slow methods is no longer needed to transport paper files from place to place. Overall, high priority items are taken care of quickly and man-hours are reduced in getting documents through the approval process. Also, all documents are automatically placed in the proper electronic folders when finished without employees needing to worry about physical filings.
- System Utility: not only were label approvals being routed, but the label routing system also was put to use to route other label-related items such as image updates, new requirements documentation, etc. This also created a reduction in waste and paper usage by making the majority of label-related tasks paperless.
- Label Template Volume: another benefit is the ability to create templates for use with multiple products. One manufacturer reported that there was about an 80% reduction in the number of labels requiring control since templates could be approved for use with a number of products.
- Availability of Documentation: while lost documentation isn't usually a major issue, frequently paper files end up in a pile of other documents and are forgotten until the due date approaches. This causes the approval process to lag.

"A process that was once linear now becomes parallel through electronic routing. This saves time by eliminating the need to move a physical file from place to place..."

Risk and Error Reduction

- The ability to reduce or remove human intervention from a process invariably reduces risk by improving accuracy. Think of all the places in the process where human intervention takes place allowing human errors to be introduced. Table A shows how replacing manual with electronic methods in the labeling process can result in error reduction.

PROCESS	Manual System	ELMS	Comment
Label Design	Design Errors	Chance of error reduced up to 80%	Labels are designed as templates and not one for one. The likelihood of errors in a manual system is increased due to the added volume.
Label Approval	Approval Errors	Chance of error reduced up to 80%	Same as above.
Storage and Control	Control Errors	None	Management of physical inventory inherently introduces known error rates for accuracy.
Printing	Data Entry Errors. 6∂ Study shows .5% of all batches impacted.	None assuming integration with validated systems.	Manual keying of data introduces known error rates.

Table A. Opportunities for error reduction from Electronic Label Management System (ELMS).

Return on Investment

- ROI Measurement: the primary driver for ELMS is usually to meet compliance needs; however, Return on Investment (ROI) can and should always be factored into any significant investment. Table B is a tool that may be used to help identify the value of an ELMS investment.
- Cost of Non-Compliance: this cannot easily be objectively measured. Are there significant efficiency improvements and waste reduction benefits from implementing an ELMS? Yes, de

finitely. In today's regulatory environment; however, for many companies, the primary driver for implementing an ELMS is compliance. According to one source, heavily regulated industries are now spending more than 40% of their IT budget on compliance.[2]

Environmental Benefits of an ELMS

- Eliminating Waste – there is less waste due to:
  - Fewer printed approval documents
  - Fewer printed audit documents
  - Fewer required test prints
- Space and Equipment: paper label control systems can require significant in-house storage space as well as increased supply costs due to high volumes of printed label documentation. The cost for storage of important paper files is exacerbated by the need for fire-proof and climate-controlled conditions. Access and other administrative controls and procedures also must be in place to accommodate a paper/manual method. An electronic file system saves time, facilities, equipment, and supplies. With an ELMS, these considerations have already been built into the required architectural design for computer systems management.
- Centralized Global Storage: without having to keep multiple copies of documents in geographically separate locations, if the ELMS can be centralized, rather than purchasing separate servers for each manufacturing location, all sites can share data in one server environment.
- Label Design and Print Licensing: if the ELMS is internet-capable (i.e., available through a web browser) it helps contain costs because the requirement for a separate software license for each machine that will be used for printing or designing labels may be reduced. Perhaps only one user license is needed and all connected workstations can work off the application server.

Other Risk Considerations

Although the benefits of ELMS will likely outweigh the risks depending on factors such as company size, number of products etc., it is important to recognize some of the more

Item	Current System	ELMS	Benefit	Calculated Saving
Design	One-to-One Label	One-to-Many	Stored approved templates reduced by up to 80%	
Approval	File Transportation	Electronic Process	Movement of paper from place to place	
Printing				
Pre-package Handling	SOPs, storage, and inventory control costs	N/A	Electronic system requires no inventory management and related costs	
Pre-package Control	SOPs, Planning/ Scheduling	N/A	No inventory means no need to plan and schedule	
Pre-package Movement	SOPs, material handling operations	N/A	No need to move pre-printed labels from storage to the packaging area at time of packaging	
Pre-package Approval	SOPs, QA Review and Release	N/A	Use of validated systems precludes the need for active approval at of labels at time of packaging	
Other Add other items as they apply. Do not overlook the fact that there may be multiple sites benefitting				
Cost of Non-Compliance				
Cost of current and future systems(s) –				
Total Cost of Ownership (TCO)				
Opportunity Costs				
TOTAL				

Table B. Quantifying potential return on investment from an Electronic Label Management System (ELMS).

impactful risks of electronic systems so that they can be mitigated effectively. Be aware that the system development life cycle should include a formal risk assessment process to identify, measure, and appropriately mitigate specific risks.

Some of the risks associated with an electronic label management system include:

1. Complexity: technology solutions are typically more complex than manual systems. Training and proper resourcing can mitigate this risk.
2. System availability: short term system interruptions may be expected due to electrical and other environmental issues, as well as due to scheduled outages for maintenance.
3. Data Loss: perhaps the most critical risk of using ELMS is the possibility of losing data due to a system failure. Technology available today permits sharing of data among databases set up in different locations. The concept of data replication provides a viable risk mitigation strategy. If a company produces labels in multiple locations across the globe, replication of all template and product data among databases on multiple servers can provide for quick and efficient disaster recovery. With data replication, the label and product information can be backed up as frequently as once every 30 seconds on a continuous basis. Data replication can greatly reduce or eliminate the possibility of losing large amounts of data in case of a sudden system outage that may occur in between backup sessions.
4. Support: having quick access to the right resources is important when real-time, in-line, business-critical electronic labeling systems are in place. Strong vendor relationships and well-trained in-house resources can help to mitigate this risk.
5. Data Corruption: another concern surrounding a fully electronic ELMS is data corruption. Should the network or a workstation become exposed to malware or other viruses, or should an outage happen during a process that causes a saved file to be corrupted or inaccessible, backups can restore the database and subsequent label printing system back to its most recent uncorrupted state.
6. Validation: although it does not represent the level of concern or risk it once did, system validation is still a major undertaking and should not be considered lightly. Today, using a risk-based approach, the burden of validation and Computer System Life Cycle (CSLC) maintenance is well understood and more reasonably addressed than in the past. An application that is assessed to be in the COTS[4] category (configurable software) can be "validated" with less effort than in the past using a practical approach and leveraging the supplier's documentation and compliance awareness.

What is the Regulatory Landscape and How Does it Relate to "Green" Initiatives?

Many of the regulations and requirements of the industry have changed to include specifics about electronic data and record keeping. With a more concrete picture of what is required, manufacturers and distributors, as well as solution providers have been enabled to shift from manual to electronic systems throughout the supply chain because the compliance requirements are becoming clearer. Provided that the specific guidelines and regulations are met, many companies have been able to realize the benefits of moving to an electronic labeling process. Enforcement and global infrastructure discussions aside, it is safe to say that most, if not all, life science product manufacturers and distributors recognize the need for and have been or are in the process of implementing product serialization and UDI capable systems.

Current State of Regulations

Below is a short list of some of the global current and to-be compliance considerations and a brief discussion of their present status.

- 21 CFR Part 11 Electronic Records / Electronic Signatures[3]
  Status: there is no recent change.

21 CFR Part 11 has been in place for many years now. Its level of enforcement has had stops and starts; however, FDA expects that any upgraded or newly implemented system will be compliant. Section 11.1 paragraph (e) states "Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection." As computer systems have become more prevalent in industry, electronic labeling has evolved and is now being developed around the specific needs of FDA regulated companies. ELMS capable of complying with 21 CFR Part 11, Annex 11, and other regulations are now available.

- California Senate Bill 1307
  Status: this law has been passed, not yet being enforced.

This law essentially states that 50% of a company's pharmaceutical products coming into the state must incorporate a unit-level interoperable electronic pedigree by 2015 and the remaining 50% by 2016. The law may be overridden by an equivalent Federal law. The most recent draft of a U.S. Senate Bill currently sitting in the Senate is not sufficient according to feedback from one of the California Board of Pharmacy members who wrote in part:

"We are by no means satisfied with the current form that the draft proposal takes, and believe it represents a significant step backward from the California model for electronic pedigree/track-and-trace. We are especially dismayed by the additional delay that is built into the various stages of the proposal. We believe regulators and the industry can and must do better than this, and that the public has a right to demand more."[4]

- U.S. Senate Bill 959 S. 959, "Pharmaceutical Quality, Security, and Accountability Act" (PQSA)
  Status: this bill has not become law.

A version of this bill may be expected to become law sometime in 2014 (in our opinion). As of this writing, this bill calls for a phased approach that eventually achieves unit level pharmaceutical product tracing over a ten-year period. What eventually will be passed may not be known for several months due to the legislative process.

- European Union – European Medicines Verification System

Although there are various country regulations with differing requirements, there is movement toward a technical track and trace model that will become the standard- at least for Europe. The technology infrastructure is expected to be tested and available for use sometime in 2014.In a recent article press release on Microsoft.com, it was written that "Microsoft and its Windows Azure cloud platform has been selected to power the new EU-wide European Medicines Verification System (EMVS) that will be developed and operated by Solidsoft, a Microsoft Gold Partner. The EMVS is the solution put forward by the European Stakeholder Model (ESM) Partners – a body that represents the majority of the European pharmaceutical industry to combat the growing problem of counterfeit medicines sold across the continent."[5] Trials are expected to begin in the coming months.

Although the regulatory landscape is still very foggy and fractured, due to the general direction and perceived or real deadlines, many pharma companies have begun to implement or build systems that they believe will comply.

So What Should We Be Doing Now?

As Mr. Dirk Rodgers pointed out in his RxTrace blog post of 14-FEB-2011 *Attributes of a Global Track and Trace Application*, "The goal is to make investments today that will be flexible enough to accommodate existing laws around the globe *and* whatever ultimately might or might not happen in the U.S., the E.U. and elsewhere. To accomplish that, 'flexibility' is the key word and the key attribute."[6]

1. Identify the Technology

Choose the solutions and solution providers who will together deliver a complete system. Everyone's environment is different so planning and thought must be given to a wide array of items including serialization software, printing software, printing hardware, vision systems, intranet and internet infrastructure, and more.

In today's world of electronic systems, it seems that nearly all "new" systems require multiple other systems to "talk" to one another. So, tight and timely integration is a key to success as well. Think about the system responsible for maintaining the repository of serial numbers and how it must interact with other hardware and software on the packaging line. Data spawned in the system responsible for creating the serial number may need to be merged with other product and lot information at print time. The serial number and its corresponding lot-related data may then need to be sent to another system for aggregation to the next layer of packaging. At the same time, perhaps a vision system must confirm legibility of the values, other data, and images on the label and so on. In addition, there may be (and eventually there will be) a system external to the company that requires serial numbers to satisfy ePedigree track and trace requirements. The database associated with whatever global track and trace system evolves must be updated at time of product shipment.

Product serialization and the aggregation of serial numbers converts what might have been thought of as individual steps in the packaging process and binds them together as a continuous process flow. It will no longer be a relatively simple process to remove and replace serialized defective units. The processes of disaggregation and re-aggregation will need to be well understood and adhered to by everyone involved in the packaging process including; supervisors, engineers, maintenance technicians, mechanics, line operators, and others.

Figure 5 shows how the integration of disparate electronic systems might bring about the delivery of an ePedigree beginning with the assignment of serialization at the lowest saleable unit.

2. Apply Good Project Management Practices

The project plan should consider task ownership so that there are clear expectations of who will deliver what and when. Although this consideration is universally applicable to all elements of the project, the bottom line is that the delivery of the system including all software, hardware, documentation, and on-going support and maintenance must be well understood and agreed upon- in writing. For example, when there is a system error; who will respond and in what time frame? Keep in mind that when the serialization system becomes unavailable, packaging will stop, at least for a short period of time. Also, given the business-critical nature of the system, business resumption and disaster recovery plans must be developed, tested, and available when the system goes live. Figure 6 is a helpful high-level planning tool for a serialization project.

3. Apply GAMP 5 Risk-Based Approach

During the project planning and ultimate implementation of a structured serialization/e-Pedigree/track and trace program, *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems* considerations should drive decision-making. Immediately upon the formalization of a systematic serialization approach within an organization, it then becomes subject to standard GxP quality management system requirements. So embedding the guidance throughout the process from beginning to end is highly recommended.

"New concepts are being developed and applied, including science-based risk management approaches, a focus on product and process understanding, and the application of quality by design concepts."[7]

So where do we start from a systems validation perspective? We can begin with gathering the essential requirements of the "to-be" solution. Boil them down into manageable, clearly stated user requirements. In this case, we might begin by parsing out a regulation and converting the system-related verbiage into user requirements terminology familiar to others in our organization. From there, the evolution to the associated functional requirements is a natural one. This will deliver a system definition that is logical and traceable within our internally approved life cycle documentation package. Also, it will support an audit process leaving little doubt that the company has taken an approach and performed due diligence specifically aimed at addressing the regulation(s) in the design of the system.

So, for example, we might read from California's SB1307:

"This bill would instead, on and after January 1, 2015, define a pedigree, as specified, and would revise the information required to be contained in a pedigree to, among other things, include a specified unique identification number."

And combined with the above…

"The bill would require the board to promulgate regulations defining the circumstances under which participants in the distribution chain may infer the contents of a case, pallet, or other aggregate of individual units, packages, or containers of dangerous drugs, from a unique identifier associated with the case, pallet, or other aggregate, if certain standard operating procedures are complied with and made available for the board to review."

Although because of the writing style, these excerpts are difficult to parse (unlike, for example, the point-by-point language seen in FDA's 21 CFR Part 11), several user requirements may result including ones that may read:

- *"The system shall be able to assign a unique serial number to each package unit beginning at the lowest saleable individual package unit level."*

  And

- *"The system shall be able to assign a serial number to each packaging level in order to "aggregate" packaging units into containers holding a number of smaller serialized package units.*

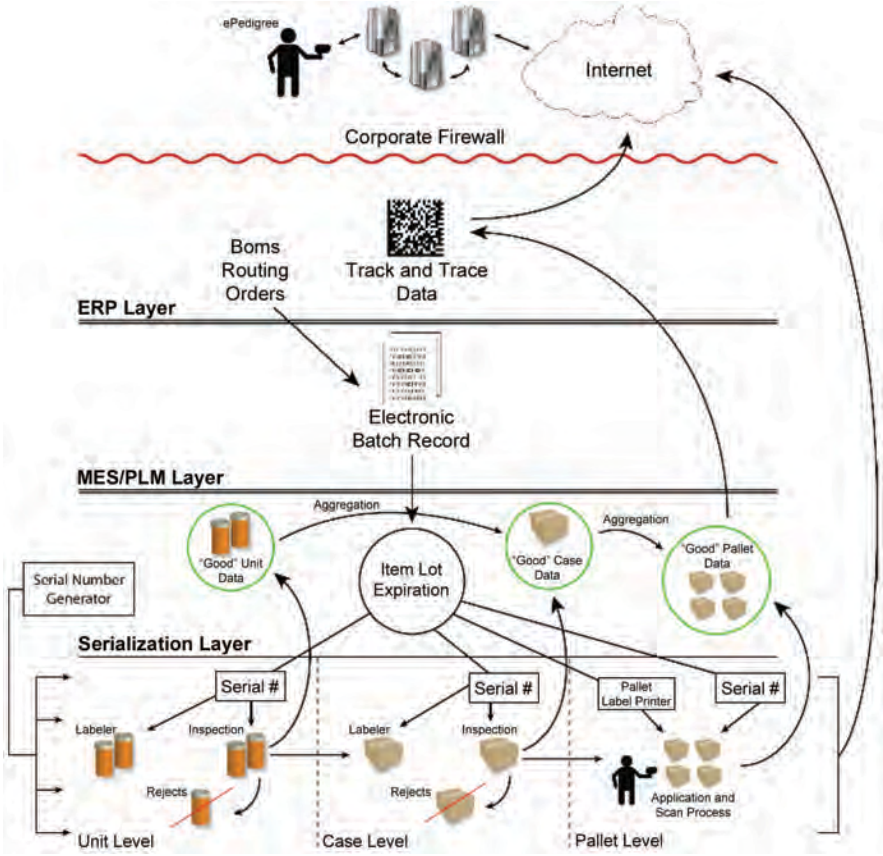

Figure 5. Serialization data and process flow.

Of course, not all of the system requirements will be gleaned from a review of the regulations. So, in addition to the user requirements focused specifically on meeting the regulations, additional requirements will need to be gathered and documented clearly describing our internal users' expectations for the delivered system. Examples of requirements for this group may read similar to these:

- *"The system shall be able to monitor availability of serial numbers and notify an operator when a 'low level' limit is reached."*

  And

- *"The system must be able to 'read' all serial numbers applied by scanning with appropriate equipment and immediately reject defective units and notify operator(s) when illegible serial number(s) is/are encountered."*

Phase	Description and Elapsed Time	Additional Detail and Comments
1	Project Planning Team Identification and Establishment 30 Days	Participants of the Track-and-Trace Serialization Team must include knowledgeable staff from the following departments (at minimum): - Operations - Information Systems/Technology - Quality/Regulatory - Engineering - Purchasing - Customer Relations
2	Serialization Objectives Established 30 Days	It is critical to understand the objectives of your organization with the adoption and implementation of serialization at the unit level. Items to consider in this phase are: - Knowledge of existing regulatory requirements - Strategy for type of serialization to be used (e.g. acceptability of inference,GS1 Datamatrix as standard - Understanding customers' needs associated with serialization and marketplace impact - Maintenance, retrieval, and archival of data - Determining ownership and responsibilities of serialization and associated tasks - Agreement on accepted regulatory assumptions (e.g. inference, inoperability) - The system must be able to provide serial numbers with no chance of duplication. - The system must be able to link packaged units from lower to higher levels such as from carton-to case and case-to-pallet such that the existence and location of a given lower unit may be inferred from that of the higher unit.
3	Evaluation of Existing Resources, Equipment, and Processes 45 Days	A thorough review of existing expertise must include the following: - Internal knowledge of serialization options and associated challenge - Does existing staff possess adequate knowledge to successfully implement a serialization solution, or will outside resources be required? - Will software be developed or purchased from a supplier? - What SOPs will be impacted with the implementation of serialization? - What equipment will be updated (if any)? - Does existing printing equipment possess the appropriate capabilities? - Are vision systems installed and capable of properly detecting applied symbology? - Do all areas throughout the facility, including warehousing and distribution activities, have the appropriate barcode scanning capability to read and collect accurate data?
4	Implementation Strategy 45 Days	This phase should include consideration for: - Identification of facility or facilities that will perform serialization - Identification of line or lines to be added and/or updated - System design and structure, including URS Development - Specification development to ensure fitness for intended use - Supplier audit and selection - System integration requirements - Data management and maintenance - Quality Risk Management assessment associated with ICH Guideline Q9
5	Equipment and Software Additions and Updates, including Integration 90 Days	Additions and updates will include: - Impact assessment on Computer System Validation framework, including 21 CFR Part 11 compliance - Samples provided to equipment suppliers and FATs performed - New/updated labeling equipment installed and qualified - New/updated software validation installed and qualified - Customer and product specific process validations updated and executed
6	Update Procedures, Implement, and Train Employees 60 Days	These revisions will include: - SOP revision and creation - Transfer of responsibility of the system and equipment to the users - Finalize and approve change control documents - Creation of Preventive Maintenance and understanding of potential of unscheduled maintenance
7	Pilot Testing 120 Days	Robust pilot testing must be performed including the following: - Complete documentation of each test case with expected outcomes and actual results - Assurance of aggregation accuracy from genesis throughout lifecycle (parent, grandparent, child) - Verification of proper label generation and application - Assurance of proper data integration throughout process - Introduction of defects to demonstrate the system is capable of identifying, notifying and preventing duplicate, missing, and falsely aggregated numbers from entering the supply chain - Defects identified and documented, including documented Corrective and Preventive Actions (CAPA) - Management of required system changes
8	Final Procedural and Equipment Updates 30 Days	Although the ideal situation would include a Pilot Testing phase that resulted in 100% accuracy, a realistic plan must expect adjustments to both procedures and equipment.

Figure 6. Serialization project tasks and timeline.[8]

The serialization project must be considered a part of a much broader project aimed at delivering a full ePedigree solution. Without consideration for how the association of a unique serial number for each saleable package unit fits into the broader goal of ePedigree, we may not provide for a fully effective and compliant system as we attempt to provide for fast and accurate track and trace capabilities.

Once the requirements have been gathered and reviewed, we will use standard internal procedures to complete the system design. The design and build processes will follow our internal Computer System Life Cycle (CSLC) defined in local procedures.

From Section 7 of *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems*, "Although the responsibility for compliance with GxP regulations lies with the regulated company, the supplier may have considerable involvement in the process."[8]

It makes sense, therefore, that serialization project leaders take advantage of the fact that there may well be suppliers capable of providing a significant amount of documented testing and evidence of a system's fitness for use in the industry from a compliance as well as from a functional perspective. It is strongly recommended that external partners considered for selection to assist in any portion of the development of the serialization solution be vetted for their ability to address regulatory requirements. Refer to *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems*, Section 7 Supplier Activities, for a detailed discussion on this aspect of the process.[8]

At a high-level, the life cycle approach for a serialization project may look like the one shown here in Figure 7.

At the beginning of the project, a list of related questions should be created and reviewed such as:

1. Can we leverage the vendor(s) testing? If so, to what degree and how much internal documented testing can thereby be reduced, if any?
2. Have we performed a good risk assessment taking into consideration business and cGMP requirements?
3. Will the validation process merge well with system expansion to eventually include full track and trace?

With GAMP® 5 as a guide, other topics to consider include:[7]

- How the system will be handed over to the users
- How the system will be measured and monitored from a performance perspective
- How incidents will be documented and corrective and preventive measures will be captured and coordinated
- How system changes will be managed
- How system audits will be conducted
- How electronic records will be maintained, retrieved, and archived

Conclusion

Assuming that a manufacturer, distributor, or dispenser of a medical drug or device may require new technology to build an electronic label management system, one must assume that any system or major component thereof will be capable of delivering on all compliance requirements. Most, if not all life science companies today follow internal procedures to assess new systems or upgraded systems for compliance.

Electronic label management systems capable of meeting challenging regulatory requirements using current technology standards are available to pharmaceutical companies today. Although not typically viewed as a high-impact cost-reduction opportunity, the hidden costs of staying the course with older technologies incapable of complying with existing regulations such as 21 CFR Part 11, Annex 11, as well as the California Rule and others may be viewed as prohibitive or unwise.

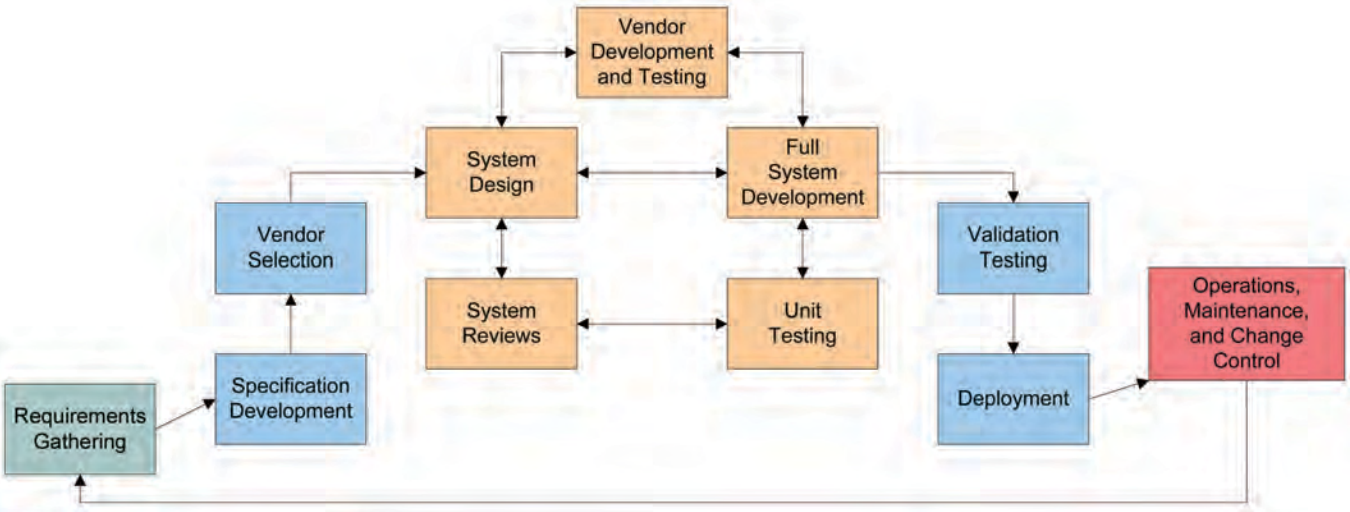

Figure 7. Computer System Life Cycle Management (excludes decommissioning).

We know that labeling has traditionally been a hot button item for auditors and that labeling errors have historically been the most common cause of product recalls. Today, there are commercially available systems that offer compliance, cost, and "green" advantages that had not been available only a few short years ago and they should be considered by companies looking to improve in the label design, approval, control, and print areas.

Employing a combination of committed and capable resources along with today's technology, good project management practices, and a practical risk-based GAMP® 5 approach, achieving compliant labeling processes, including serialization, is possible. However, if up to now an organization hasn't yet begun, the timeline may be unachievable and/or much more costly than it might have been with an earlier start.

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About the Authors

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Sustainability and its Relevance to the Pharmaceutical Industry

by Rob Bowen

This article demonstrates the relevance of sustainability to the pharmaceutical industry and presents a viable path to achieving sustainability in the industry.

The principle of sustainability, or more correctly, sustainable development, has existed as long as humankind has existed – maintaining "the capacity to endure"[2] has been the abiding focus of us as tribes and as an industrial entity – the latter, of course, for not quite so long. Currently, sustainability has been the word reference for the wide range of measures considered necessary to help avert issues associated with climate change (Figure 1), the increasing world population (Figure 2), and the effect of carbon on the atmosphere. Other associated equally relevant topics include "eco-friendly" and "biodiversity."

> ***Sustainability:*** *development that meets the needs of the present without compromising the ability of future generations to meet their own needs.*[1]

The article has been written around the premise that there is a viable path to achieve sustainability that responds to all of the guidelines of the industry and is as relevant to the pharmaceutical industry as it is to any other industry. Indeed, ethically, more so since the pharmaceutical industry is focused on maintaining or improving patient health.

Background

First Recognition

During the 1950s and 1960s, a growing number of western academics and new thinkers became concerned at the post war explosion in population (Figure 2), often referred to as "the bulge," and its effect on the global capacity to maintain growth economically and provide the resources to match the increasing requirements. This, naturally, also was a period from which our own industry benefitted substantially through the availability of increased research funding and new markets, and in that way, itself contributed to the population increase through the enhanced life expectancy that we now enjoy – and expect.

The need for infinite growth and resource also were academically associated with environmental concerns about the increasing effect on the earth's atmosphere through use of carbon rich fuels and processes and what appeared to be the effect of this on a significant reduction in the protective ozone layer through the addition of greenhouse gases.

The groundswell of concern and opinion gained mainstream political recognition through the publication by the influential Club of Rome of the book "Limits to Growth" in 1972.[3]

Global Pledges and Withdrawals

The political impetus reached its head through the United Nation's World Commission on Environment and Development, "The Brundtland Commission's," publication of the report "Our Common Future"[4] in 1987. It is notable in pharmaceutical industry terms that Dr. Gro Harlem Brundtland,

the former prime minister of Norway and chair of the Commission, was Director General of the World Health Organization between 1997 and 2003.[5] She is currently Special Envoy on Climate Change for the United Nations Secretary-General Ban Ki-moon.[6]

The Kyoto Protocol to the United Nations Framework Convention on Climate Change (UNFCCC) of 1997 was accepted by all 192 parties, although exceptions to full recognition were Andorra, Canada, South Sudan, and the United States, who to this day do not fully accept, or have withdrawn from, either the intent or the detail. As of the date of this article, the USA remains in a position of signatory, but without ratification of the protocol. Canada withdrew from the protocol renouncing its membership in December 2011 and is the only significant nation sitting outside the commitments.

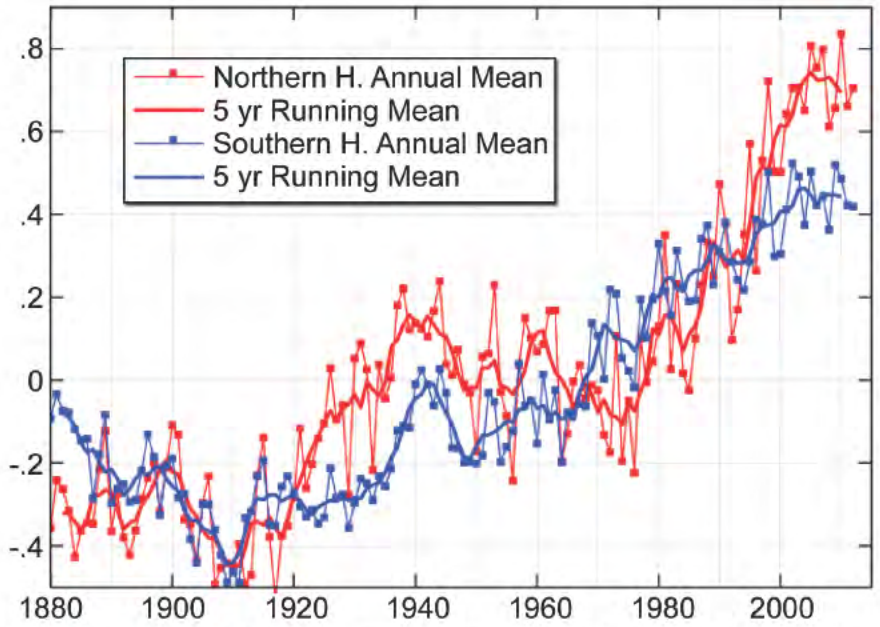

Figure 1. Annual Mean Temperature Change for Hemispheres: NASA Goddard Institute for Space Studes – Jan 2013 Update.

The protocol, among other things, was based on yearly percentage carbon reduction or Green-

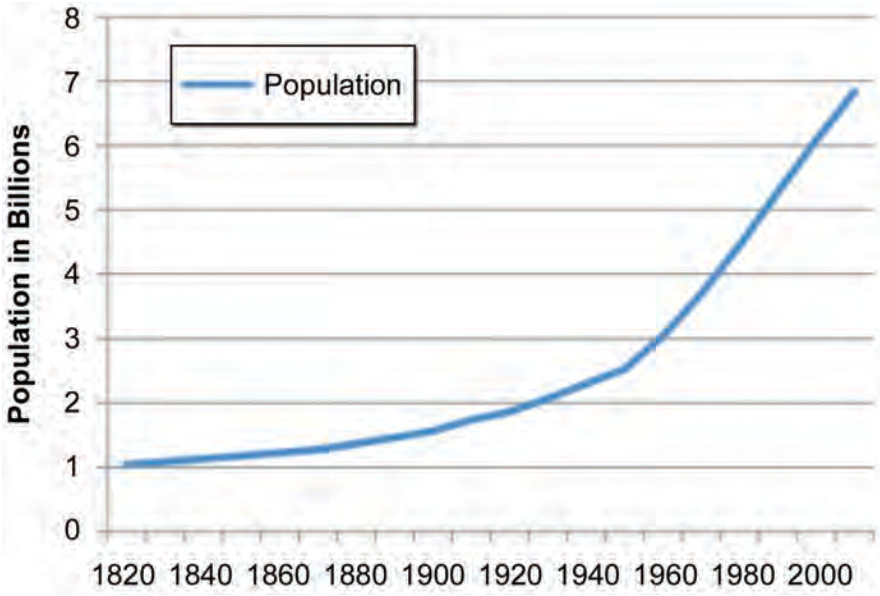

Figure 2. World Population: based on Angus Maddison estimates, Groningen Growth and Development Centre, Netherlands.

house Gas (GHG) targets commonly set on a 1990 base. The protocol also set up the premise of carbon trading. The first commitment period was 2008-2012. The carbon reduction targets were extended in 2012 to cover the period 2013 to 2020 with binding targets accepted by 37 countries, including Australia and the European Union (currently 28 countries7 with a candidate and potential candidate addition of a further eight countries).

Early Adopters and Environmental Assessment

In parallel with the political adoption and its subsequent legislative effect (see below) in many countries, particularly, and inevitably, those of the Kyoto accepters, there have been several prior and subsequent initiatives providing methodologies for environmental assessment and lifecycle assessment. The ISO 14000 series provide guidance on environmental management and the quantification and reporting of greenhouse gases. Some notable facility environmental assessment and rating methods are:

- Building Research Establishment Environmental Assessment Method (**BREEAM**): this, the first significant method, was established by the UK, then state-owned, Building Research Establishment (BRE), now privatized as BREGlobal (BREG). Commencing in 1988, with its first release for commercial office building in 1990 since expanded to cover all building types either directly or via a bespoke method, it uses a scientific method applied by trained third party assessors using score sheets to award on the basis of "Pass," "Good," "Very Good," "Excellent," and "Outstanding." Assessments are carried out at design stage and subsequent to construction. BREG claim in excess of 200,000 buildings with certified BREEAM assessment ratings and more than a million registered for assessment. There is an accredited professional (BREEAM AP) qualification. Assessment is required for new UK government buildings. www.breeam.org.

- Leadership in Energy and Environmental Design (**LEED**): pilot tested by the US Green Building Council (USGBC) in 1998 and launched in 2000, LEED ()is the primary US assessment and rating system. As with BREEAM, it uses a scoring system to rate buildings and sites and awards on the basis of Certified, Silver, Gold, and Platinum. USGBC certified its 10,000th building in August 2011 and LEED registered and certified projects number more than 100,000 globally. Assessment can be through self or third party assessment by a trained professional with additionally an AP, Associate, and Fellowship program operated by the USGB Institute. www.usgbc.org/leed.

- Comprehensive Assessment System for Built Environment Efficiency (**CASBEE**): this self or third party assessment tool, (CASBEE), is Japan's environmental method for building assessment and has been developed by the Japan Sustainable Building Consortium (JSBC) to take into consideration issues and problems peculiar to Japan and Asia. The method uses two factors, Q (built environment quality) and L (built environment load), assessed separately. A five-level star based scoring system is used, with a score of level 3 indicating an "average." As with BREEAM and LEED, an AP qualification is available. JSBC reported just under 7,000 buildings assessed by the end of 2011. www.ibec.or.jp/CASBEE.

Lifecycle Assessment (LCA) is a tool used in assessing the environmental impacts of a product, process, or service from design to disposal.[8] LCA software is available from several sources, including those noted above, as either add-on services or standalone packages providing assessments for site and facilities as well as for individual product assessment. This cradle to grave evaluation is essential to archive correct sustainability planning.

The Business Case[9]

The business case for involvement in sustainability, as time

passes, is becoming increasingly attractive as the cost options become more transparent and the adoptive countries introduce legislation that enforces sustainable practices. Further, shareholder concern, the availability of ethical investment funding, and intellectual worker expectation/satisfaction all figure in making engagement worthwhile, and in some cases, unavoidable.

To many, it is a case of "how far should we engage?" At board level, there appears to be either full acceptance or blunt resistance with many companies engaging totally and others only doing so under legislative duress.

Ethical Investment

There has been a notable rise in ethical consumerism even during the world recession. The expectation of purity of source and ethical validity of a product, whether that is shares or the final product, is increasingly capturing the attention of the rising world middle class. A preparedness to pay more for, or demand, a product that is not savored by purely the cheapest route is apparent. This is picked up by even the hardest line of market driven product. The following quote is from Pepsico's Indra Nooyi, Chairman and CEO, "Our belief is that our financial success — Performance — must go hand-in-hand with our social and environmental responsibilities – our Purpose."[10]

Legislative Engagement

The medium of legislation is inevitably the most powerful tool that can be applied to ensure sustained action (forgive the pun).

The danger for states is that the more onerous they make legislation, the less likely it is that the global corporations, the most significant force in our industry, will wish to invest, unless there is any other incentive, or unless, of course, the market is too large to resist and the import burdens likewise too onerous; so there is a balance to be struck. So to enforce political will group action has shown to be the strongest medium.

Having accepted Kyoto in its entirety, it fell primarily to the European Union (EU) to lead in imposing legislation on its member states; it has to be noted that both Singapore and Australia applied early legislative nooses also; in Singapore's case, successfully balancing it against a low corporate tax profile.

The EU applied what is known as the 20-20-20 target through three key directives; Energy Performance in Buildings (2002/87/EC) – EPBD – in 2002, the Emissions Trading Scheme a year later, referred in the next section, and the Renewable Energy Directive (2009/28/EC) in 2009. The energy performance directive requires the member states to achieve a 20% reduction in energy usage on 1990 levels and a similar reduction in greenhouse gases by apply minimum energy performance standards to new and large refurbished buildings using an energy performance calculation methodology and expecting displayed energy certification. It also expects third party inspections of air conditioning systems and boilers on a regular basis to ensure their efficiency. In terms of renewable energy, the final 20-20-20, the target for the EU as a whole is 20% by 2020. Countries are weighted against their capacity with, for example, the UK expecting to provide a 15% reduction.

For example, to achieve the EU expectations, the UK legislates and controls on three fronts: legislation, regulation, and monitoring. Changes of government and the world recession have had their affect in terms of method, but the target remains and they are assessed by an impartial committee – the Committee on Climate Change – that has specific annual reporting criteria. The accompanying legislation ensures that companies must report on energy usage; planning codes in some areas expect environmental assessments and otherwise expect interaction with the government agencies responsible for environmental matters – 1:200/1:1000 year flood attenuation, biodiversity response, finance for green transport projects, car and bicycle provision, sustainable construction, etc.Mandatory Building Regulations, which control build quality and performance, are being tightened per three years to achieve the target carbon take through expectation of submission of mandatory Simplified Building Energy Model (SBEMs), a government approved third party energy use assessment method with a requirement for a partial renewables response, at submission stage which must be proven on completion. This includes pressure testing of non-domestic (industrial) buildings and provision of Energy Performance Certificates (EPSs) on completion. This affects all new construction including retrofits. Retrofits over 1000 m2 (c10,000 sq ft) – it is anticipated that this will be reduced over time – attract scrutiny of the rest of the facility with an expectation of upgrades to a particular level to meet energy reduction criteria.

The above is, of course, related to the new construction and retrofitting of buildings and does not directly affect the manufacturing processes. These in legislation terms, again taking the EU UK model, are based on a carrot and stick approach when it comes to sustainability, primarily focussed on energy reduction and renewables. The current primary industry incentivization tool in the UK is the Renewable Heat Incentive (RHI) which aims to provide a long-term financial incentive. The objective of the RHI is to significantly increase the proportion of heat generated from renewable sources by providing a tariff based subsidy, payable for 20 years, to eligible renewable heat generators.

So, depending on where you are in the world, sustainability in the energy save and ecological protection senses may be legislation controlled potentially to the short term investment disadvantage of local players and at the pick and choice of the global corporations. In this respect, there is an

argument that the healthcare should take a responsible lead as a long term player accepting the health principles implied by principles of sustainable development.

Carbon Trading

Emissions, or carbon, trading, as set out in Article 17 of the Kyoto Protocol, allows countries that have emission units permitted them not "used" to be traded to countries that are over their targets.[11] Carbon credits (one credit = one metric ton of CO_2), or emissions permits, are available to trade also through domestic or regional emissions trading schemes working to overall nationally set targets.

The largest trading scheme is the EU ETS, 2003/87/EC – empowered since 23 Oct 2003, and described as "the cornerstone of the European Union's policy to combat climate change and its key tool for reducing industrial greenhouse gas emissions cost-effectively."[12] This works on a "cap and trade" principle, as do most schemes. A cap is set on the total amount of greenhouse gases that can be emitted by all participating parties. "Allowances" for emissions are then auctioned off or allocated for free, and can subsequently be traded. In the EU ETS's first year, 362 million ton of CO_2 were traded on the market for a sum of approximately $9.7 billion, and a large number of futures and options. Much like a stock market, companies and private individuals can trade through brokers who are listed on the exchange.

In the USA the Environmental Protection Agency (EPA), a federal body, has been administering cap and trade schemes since 1995 including the Acid Rain Scheme and the NO^{13} Budget Trading Program. The Clean Air Interstate Rule (CAIR) was launched in 2005 aimed at reducing power plant pollution. California has had a greenhouse-gas reporting requirement in place since 2008 and launched a unilateral carbon trading scheme in 2012 commencing in January 2013 aimed at reducing greenhouse gases to 1990 levels by 2020 and ultimately achieving an 80% reduction from 1990 levels by 2050.

China launched its first carbon trading scheme piloting it in Shenzhen province with expansion to initially include Beijing, Shanghai, Guangdong, Tianjin, Chongqing, and Hubei with the intention of it being taken nationwide in 2015/16.[14]

How Does This Affect Our Industry?

Now is a time of change in many areas. These changes affect the way that we design and operate our facilities to a significant degree.

The worldwide recession brought with it changes in company fortunes which mixed with an on-going rebalancing of global wealth, together with a decline in the product pipeline, have combined to place significant challenges on the traditional pharmaceutical companies, "big pharma." They have been further challenged by the generic manufacturers and the CMOs with this declining pipeline as products come off patent making a focus on cost of goods inevitable; a condition that has affected OSD products for some time and now, of course, includes challenges from biosimilars. Further, new product is emerging that is developed in different forms and by significantly different means than the API/chemical excipient processes of "traditional" chemical based products. Likewise, the advances in capability to increase titre mean that the biologics manufacturers have the opportunity to rethink their manufacturing processes.

There is inevitably an issue with development cost and the effort and expense in relicensing products has been prohibitive. This tends to mean that changes in process have to be hard fought or just not worth consideration. This has stood as a barrier to new development for each of the three enterprise formats.

This has meant that we have been tinkering with continuous processes and closed processing for some time without getting serious about the implementation of either with some notable exceptions. This has made sustainable options difficult to achieve as open or semi-closed product in large, cumbersome facilities based on equipment responding to old, yet admittedly tried, chemical formulae or biological set-ups dating back in the case of the former to the late 19th or early 20th centuries; or the latter to just post mid-20th century is still the norm for much of our industry; as are open fronted fume hoods/cupboards in research.

There is now the opportunity, whether it be in Research and Development (R&D), development research, Clinical Trials (CT), scale-up, Oral Solid Dosage (OSD), biopharma, or Over the Counter (OTC), through taking a leading role in the on-going science, technology, and sustainability revolution available through developments both within our own and transferred from other industries providing significantly greater operational flexibility than that available through traditional laboratories or batch manufacture and the opportunity for, once in place, significant sustainable cost gains throughout the process. Not the least these include:

- New principles of chemical design for manufacture through the use of Quality by Design (QbD) principles
- New materials and manufacturing methodologies making process closure and/or continuous operation more accessible:
  - Smart engineering plastics as metal replacements providing smarter, simplified valving system's and smooth bio-safe connections
  - Improved equipment production techniques and design practices providing more ergonomic interfaces and safer accessibility
  - Opportunities for integration of smarter isolation systems allowing system closure as secondary, or even tertiary, containment reducing the need for further room containment

- Increased automation and robotic options, when linked with PAT identification and characterization, allowing rapid, controlled, quality assured transfer of product from one process stage to another
- Smaller, modular, flexible equipment set-ups and rigs providing the opportunity for greater interaction with the world at large
- Smarter and more visible control systems allowing more portable interfaces
- An enlightened approach to operations through the availability of additional metrics and quotas, i.e., no longer just a financial bottom line, but sometimes an energy or emissions budget in kWh, CO2, etc.
- Many of the above are accessible to all stages of drug development from the R&D laboratory through to warehousing and packaging operations providing a more sustainable approach.

There is always a cost to join, but when linked with a more open risk-based regulatory environment and with new sustainability based parties to whom companies are accountable – some are voluntary, such as rating system reviewers and internal corporate sustainability managers, and others mandatory, such as regulators and energy code officials – mean that engaging with a more sustainable approach to design, implementation, and operation is not only feasible, but available and increasingly necessary.

What Does That Mean in Engineering and Architectural Terms?

Other than our obvious engagement in the above as designers and engineers of systems, as operational engineers and architects involved in pharmaceutical process and facility design, engineering, and maintenance, we are members of a global industry that, for all the right and wrong reasons, needs to respond to the commercial pressures of drug discovery, development, and production.

So we have a set of choices – follow the mean and achieve sustainability by legislative default or engage up front in ensuring that we achieve significant improvements ahead of the game. Throughout the drug product supply chain from the way we design facilities, including the settings we place them in, to the processes we use to produce, manufacture, package, store, receive, and export use of sustainable options provides overall gain. Example areas of engagement include:

- Working with company boards in setting a sustainability policy
  - Developing a route-map
  - Providing resources
  - Promoting initiatives
  - Measuring outcomes
  - Costing ROI
  - Rewarding success
- Applying environmental management standards
  - ISO 14001, ISO 50001
- Reducing carbon take through:
  - Carbon footprinting
  - Tracing embedded carbon
  - Use of renewable energy production resources
  - Changing boiler systems to eco-friendly fuels
  - Consideration of modes of transport
- Reducing solvent reliance
  - Use green chemistry solutions where possible in development of new processes
  - Challenge and re-formulate existing products and processes
- Reduction in use of energy through:
  - Reducing airflows and room backgrounds
  - Greater use of air recycling
  - Increased use of isolation techniques
- Adopting a “no waste” philosophy
  - Consider all options for recycling both internally or through fair market means from water and chemicals to packaging and stationery
- Considering water usage and quality
  - ISO 6107 series
  - Recycling process water rather than once through
  - Use of grey water
  - Use of ground absorption techniques
- Insulating more efficiently to maintain product viability and comfort environments
  - Challenge the heat output of processes
  - Use smart heat exchange techniques and phase change materials
  - Re-use available heat and coolth efficiently and effectively
- Challenging the supply chain methodology
  - Reduce warehousing to required storage
  - Where possible reduce process steps and quarantining

Some sustainability initiatives fight against what we are used to, yet with team engagement viable, cost effective solutions may be found that retain all our expectations of secure and safe operation even in the tight operations required of, say, API/sterile production and provide significantly more cost effective means of production.

In the design of new facilities and the retrofitting of existing ones, using Building Information Modeling (BIM) 3D through to 8D techniques linked with environmental review tools, there is the opportunity to include sustainability into each of the review processes to ensure that holistically sustainable solutions are captured and the opportunities are acted on.

Naturally, it depends where you are in the world as to which sustainability practices and techniques most suit the

condition. There is a difference between, say, Sweden, Washington, South Carolina, or Singapore in cause and effect due to the environmental condition pertaining to each latitudinal location. As a simple construction design example, building parapetted buildings in monsoon zones for clean processes is probably not the most sensible solution (and there are many); run off can be most readily be captured and reused using external guttering and piping systems with less risk from the environment to the product.

So, sustainable solutions may come from advanced holistic thought and systems to the significant benefit of our industry and, ultimately, the patient we are serving.

What is the Current State of Play?

The pharmaceutical industry response: it is fair to say that much of this article is preaching to the converted; while the use of the verb "reduce" and its derivatives is a key to the viability of sustainable solutions financially and initiatives, such as those aimed at introduction of green chemicals, reducing air volumes, and use of off-the-shelf photovoltaics, for example, are pursued by many if not most pharmaceutical companies.

Who is currently doing what? The majority of operations are supporting the implementation of initiatives around sustainable approaches. The following is based on a web search for "sustainability policy." It is recognized that some of the CMOs are generic manufacturers, and vice versa, and some of both produce their own products; a line that is becoming increasingly blurred.

Big pharma: the following are the 2013 Forbes top 10 pharmaceutical companies by valuation ("big pharma"):

- **Pfizer:** (USA) http://www.pfizer.com/responsibility
- **Novartis:** (Switzerland) http://www.novartis.com/corporate-responsibility/access-to-healthcare/our-key-initiatives/novartis-foundation-of-sustainable-development.shtml
- **Sanofi:** (France) http://www.sanofi.co.uk/l/gb/en/layout.jsp?scat=671C0B72-BFB6-4E9B-9C6E-B0B021B9BB83
- **Merck:** (USA) http://www.merckresponsibility.com/focus-areas/environmental-sustainability/
- **Roche:** (Switzerland) http://www.roche.com/responsibility/sustainability.htm
- **GlaxoSmithKline:** (UK) http://www.gsk.com/responsibility/our-planet.html
- **Abbott:** (USA) http://www.abbott.com/citizenship/priorities/safeguard/environment.htm
- **AstraZeneca:** (Sweden/UK) http://www.astrazeneca.com/Responsibility/Governance-management/External-benchmarking
- **Amgen:** (USA) http://www.amgen.com/about/policies_environmental_sustainability.html
- **Lilly:** (USA) http://www.lilly.com/Responsibility/environmental-sustainability/Pages/environmental-sustainability.aspx

There is much intent and acceptance that sustainability is a serious endeavour and requires focused action. GSK stands out as the company with a stated expectation of across-the-board carbon neutrality by 2050 (i.e., not purely through carbon neutrality in energy alone).

It is important to include a further member of the "big pharma" family, Johnson and Johnson,15 as they have a strong set of sustainability policies and understanding of the contribution that these make.

Generic Pharmaceutical manufacturers: the following are drawn from a web based report by about.com on the leading pharmaceutical generics companies:

- **Teva:** (Israel) http://www.tevapharm.com/Social/Pages/Environment.aspx.
- **Sandoz:** (Germany – Novartis generics division) – while there is no link apparent on sustainability it is reasonable to assume that Sandoz division accepts Novartis policy on sustainability.
- **Actavis Inc.:** (formerly Watson Pharmaceuticals): (Switzerland) http://www.actavis.com/en/Responsibility/Environmental/Partners.htm.
- **Mylan Inc.:** (USA) no web link available on sustainability.
- **Hospira:** (USA) http://www.hospira.com/about_hospira/sustainability.
- **Ranbaxy:** (India) http://www.ranbaxy.com/csr-ehs/ranbaxy-consumer-healthcare-science/.
- **Aspen Pharmaceuticals:** (South Africa) http://www.aspenpharma.com/sustainability_1.aspx.
- **STADA Arzneimittel:** (Germany) (http://www.stada.com/company/company-profile/responsibility-and-sustainability.html.

It is reasonable to note that of the policies that stand out in the CMO group considered those of Hospira, Aspen, and Stada show a clearly apparent sustainability policy.

Contract Manufacturing Organizations (CMOs): these, as with the generics list, is not in order, but a random selection of the top CMOs from a listing for 2013-2023 forecast growth by Visiongain.

- **Lonza:** (Switzerland) http://www.lonza.com/about-lonza/global-citizenship/sustainability.aspx
- **Evonik Industries:** (Netherlands) http://corporate.

evonik.be/region/belgium/en/media/press-releases/archive/pages/news-details.aspx?newsid=11377.

- **DSM:** (Netherlands) http://www.dsm.com/corporate/sustainability/planet.html.
- **Boehringer Ingelheim Biopharmaceuticals:** (Germany) http://corporateresponsibility.boehringer-ingelheim.com/sustainability.html.
- **Dr. Reddy's Laboratories:** (India) http://www.drreddys.com/aboutus/sustainability.html.
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- **Cambrex:** (USA) http://www.cambrex.com/index.php/about/corporate_citizenship.

Awareness of sustainability appears high among the CMOs. Their need in any event is to reflect the policies of the organizations with whom they contract and, while cost is a key driver, there is a need to balance this with market expectation.

Why a Coordinated Set of Guidelines and Standards Makes Sense

Learning from each other: once accepted as a principle, sustainability is an area where we do not need to compete and the overall gains become industry rather than company beneficial through, not the least, improved public perception and company and staff pride in a responsive healthcare industry.

Baseline: it is suggested that sustainable development is adopted as an industry baseline with a set of key performance criteria set in line with, or ahead of, the current highest legislated standard and reflected through the LEED Platinum, BREEAM Excellent or Outstanding or an equivalent in an approved set of environmental assessment methodologies. Further, that LCA, also based on an approved set of principles/software bases, is generally adopted by our industry.

What is ISPE Doing, What More Can it Do, and in What Areas?

There is currently an International Leadership Forum initiative led by Dr. Thomas Zimmer considering how best to respond to sustainability objectives.

Awards: since 2009, the Facility of the Year Awards (FOYA) has included Sustainable Facility of the Year, valuing facilities on a reasonably onerous set of criteria.

Initiatives: a task team is actively engaged in the development of an ISPE Sustainability Good Practice Guide. Recent ISPE guides also incorporate information on relevant sustainable approaches, and as the current ones are updated, these will be updated to include relevant recommendations and data.

Engagement: the HVAC and Sustainable Facilities Communities of Practice (COP) are involved in the organization of conferences and development of papers and articles, as well as on-going discussion on sustainability opportunities and objectives. Several of the current 18 COPs are engaged in similar activities.

In support of this, ISPE has the opportunity to encompass sustainability as a principle across the board and work with the wider industry in advancing the very specific needs of the pharmaceutical industry in achieving successful sustainable outcomes.

Conclusion

Quoting the introductory lines of the United Nations World Health Organization (WHO) document "Measuring Health Gains from Sustainable Development:"

"Measuring health can tell us how well development is advancing the three pillars of sustainability – social, environmental and economic."[16]

Engagement in sustainable responses is significant to our industry in that the WHO cannot achieve its objectives without the drugs and drug advances we produce, so it would be somewhat unethical to consider other than producing drug products by sustainable means.

Sustainability in its broadest sense affects all areas of a company's operations, and taken to its extreme, affects business planning, operational management, drug design decisions, procurement, and material sourcing as much as it affects facility and equipment design and operation. It demands a sound technology led attitude, and applied correctly, provides the opportunity for significant financial gains, a more pleasant working environment, and greater satisfaction all round through contributing to healthcare through providing added, tangible benefit to our end user, the patient.

In facility terms, we have been operating as four teams in their development – facility operators, process designers, facility designers, equipment manufacturers – integrating these holistically, we can take the opportunity to work in a risk mapped environment using QbD principles to provide significantly improved operational processes, sustainable systems and facilities that interact both internally and externally with the environment to our joint benefits. With similar improvements across a carbon footprinted supply chain, we can show real benefit to shareholders, stakeholders, and patients alike.

The *ISPE Sustainability Good Practice Guide*, taken with suitably amended Baseline and Good Practice Guides will help in aiming to provide that opportunity for a sea change toward ensuring an ethically acceptable yet financially viable and secure pharmaceutical industry.

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About the Author

Rob Bowen is Director of Facilities Integration Ltd. (FI), a UK design consultancy based on his experience of 40 years as a practicing architect, the last 25 years of which have been working with pharmaceutical, specialist device, and food industry based clients and process focused design and management organizations. In terms of the latter, prior to founding FI, he spent 15 years with Fluor Manufacturing and Life Sciences Europe and AMEC Projects (now Morgan Sindall PS). Bowen has design team led, masterplanned, and designed R&D, manufacturing, and distribution facilities for companies including GSK, J&J, Novartis, Lonza, and Pfizer. He has consluted on the architectural elements of containment, developed bio, bio-generics, and tableting facility designs for both new and existing facilities and aided in the resolution of significant facility based FDA 483 issues. Bowen has spoken at the UK Institute of Mechanical Engineers, ISPE, Interphex, and APV Graz seminars. He is Vice Chair of the ISPE UK Central Region and Global Co-Chair of the ISPE HVAC and Sustainability Community of Practice. He has written for BioPharma Asia on the how a risk-based approach will change the face of pharmaceutical manufacturing and is responsible for two chapters of the forthcoming update of the IPSE Biopharmaceutical Facilities guide. Current work includes two masterplanning projects and a concept design for a new product facility working alongside Foster Wheeler and BPE. He can be contacted by email: rob.bowen@facilitiesintegration.com.

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Energy Benchmarking in the Pharmaceutical Industry

by Josh Capparella

This article describes the role of energy performance benchmarking in the pharmaceutical industry, explains why large variations in building performance exist and how to use benchmarking data to drive meaningful results into a successful energy management program.

You can't manage what you can't measure. This axiomatic statement holds true in all aspects of life; it is hard to manage one's weight without a scale and it's hard to manage how fast one is traveling without a speedometer. Likewise, it is hard to manage the energy performance of a building without a similar macro-level indicating gauge. There is no better way to assess the overall performance of a building than to compare it to other buildings similar in form, function, and location. Unfortunately, this is frequently an acutely difficult task to perform in the pharmaceutical sector. While tools for this evaluation do exist, they are not without their limitations as the approach for comparison is sometimes over-generalized. Facility design and layout play a dramatic part in the overall utility consumption of a facility as, unlike in the commercial sector, the majority of the energy consumption in pharmaceutical manufacturing buildings lies within the process itself and the systems that support it. Several examples will be presented to show just how profound the differences in energy consumption can be. This article will describe the role of energy performance benchmarking in the pharmaceutical industry, explain why large variations in building performance exist and how to use benchmarking data to drive meaningful results into a successful energy management program.

Commercial Building Benchmarking

In the commercial building realm, there are extensive resources available that make this data available for all to use. The Commercial Building Energy Consumption Survey (CBECS), managed by the U.S. Energy Information Administration under the Department of Energy (DOE), has collected and analyzed data for many different types of commercial buildings. The CBECS database is the most robust resource currently available, not only from the quantity of buildings in the survey, but from the vast number of ways that the data has been sliced and diced for comparative purposes as well.

The CBECS is a national survey that collects information on the stock of United States commercial buildings including energy related building characteristics, energy consumption, and expenditures. The buildings in the study incorporate all buildings in which at least half of the floor space is used for a purpose that is not residential, industrial, or agricultural. The survey includes building types that might not traditionally be considered commercial, such as schools, correctional institutions, and buildings used for religious worship.

The CBECS database has had several setbacks in recent years with the 2007 survey information being thrown out due to insufficient survey methods and the 2011 survey being cancelled due to funding cuts. Fortunately, funding has since been garnered and work on updating the survey for 2012 has recently begun. Regardless of its flaws, the CBECS database remains the best source of reliable information to benchmark the energy performance of a commercial building.[1]

It is upon this premise that the Environmental Protection Agency's (EPA) Energy Star building performance rating system has been built upon. Using the information in the CBECS database, energy performance indicator tools exist that allow users to input simple statistics regarding building

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size, type, location, occupancy and overall utility consumption in exchange for a 1-100 percentile rating that benchmarks the performance of the user's building against similar buildings. Buildings scoring in the 75th percentile or higher are eligible for the Energy Star certification. The tool compares the inputted building criteria to a normalized model to adjust for inconsistencies in form, function, and location based on the CBECS database.

Commercial buildings have a common bond in their primary function in that they are designed primarily to maintain the comfort of the occupants. Lighting and space conditioning (heating, ventilation and air conditioning) energy consumption are relatively similar and vary predictably with only a few variables. Based upon the EIA Annual Energy Outlook 2012, lighting and space conditioning account for 13.6% and 47.3% respectively (60.9% combined) of the total building energy consumption footprint.[2] The remaining consumption is allocated between various plug loads and water heating requirements as shown in Figure 1.

Since the majority of the commercial building energy consumption is dedicated to lighting and environmental comfort systems, the Energy Star tool needs only to prompt the user for a small number of inputs to be able to quickly normalize the subject building to the model and develop a highly reliable energy performance benchmark.

Pharmaceutical Building Benchmarking

Moving out of the commercial building realm into the industrial and manufacturing building classes, a problem arises. In general manufacturing, energy is also consumed to conduct whatever processes are required to make the product. This consumption frequently goes beyond just powering the production equipment itself; it also encompasses increased base building utility system requirements from additional or more stringent HVAC requirements to greater lighting intensity requirements to additional utilities such as compressed air, vacuum systems, etc. It is this manufacturing energy consumption that is highly variable and difficult to normalize within a benchmarking model. This problem is exacerbated in the pharmaceutical industry due to the need to

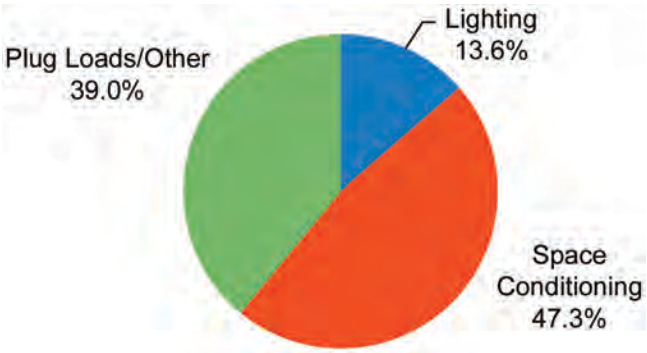

Figure 1. Commercial building energy consumption by end use.

maintain critical environments for production with respect to temperature, humidity, room pressurization, cleanliness, containment, and other contributing factors. Building HVAC loads are many times greater than the average commercial building to support these processes. As a result, overall building Energy Usage Intensity (EUI) is typically an order of magnitude larger or more. The average recently built (after 2000) commercial office building has an average EUI of 81.4 kBtu/sq. ft. (257 kWh/m^2).[3] The average pharmaceutical plant has an EUI of 1,210 kBtu/sq. ft. (3,819 kWh/m2).[4] Contributing factors to these relatively higher levels in building HVAC loads compared to general commercial buildings include, but are not limited to, the following:

- Increased airflow quantity requirements
- Increased ventilation requirements
- Increased filtration requirements
- Requirements for tighter environmental controls (temperature and humidity)

The above factors lead to higher energy consumption through increased:

- Cooling loads
- Preheat loads
- Reheat loads
- Fan energy consumption
- Dehumidification/humidification loads

Discussion regarding the quantification and analysis of the causes for increased consumption is a study in itself and is often cumbersome to calculate. For simple comparative purposes however, consider that a standard air handling unit serving an office area is going to condition and supply between two to six Air Changes Per Hour (ACPH) to the space in a variable air volume control strategy. An analogous air handling unit serving an ISO 14644-1:1999 class 8 (EU Grade C in operation) cleanroom in which pharmaceutical product is being manufactured would typically condition and supply between 20 and 35 ACPH to the cleanroom in a constant volume control strategy. This represents approximately a four to six fold increase in HVAC energy expenditure before tighter temperature and relative humidity control requirements, increased outside air requirements, and additional filtration are considered. With the additional energy consumption of the manufacturing systems and processes themselves, it can easily be seen how the overall energy consumption of pharmaceutical facilities becomes far more intensive than their commercial facility counterparts.

Based on the unique nature of the industry and the inability of existing tools to effectively gauge the performance of these buildings, the EPA Energy Star program developed a meaningful comparative tool uniquely dedicated to

benchmarking energy consumption in the pharmaceutical industry. Led primarily by energy managers from several major drug manufacturers, the Energy Star program began a pharmaceutical industry focus early in 2005.[5] From those initial efforts, the first version of the pharmaceutical industry Energy Performance Indicator (EPI) tool was developed and published at the end of 2008. Last updated in the summer of 2012, the tool seeks to normalize and benchmark facility energy performance of facilities located in the United States across three major categories:

- Bulk Chemical (Active Pharmaceutical Ingredients and Excipients) – areas where both active and inactive ingredients are prepared in bulk form, including mixing, milling and drying of powders, and the mixing of liquids, gels and creams.[6]
- Fill/Finish – all areas used for fill or finish processes or other manufacturing, production or warehousing with climate controlled environments due to product requirements. Fill/finish includes tableting, encapsulation of powders or liquids, the final packaging of the product and the filling of liquids, gels or creams in their consumer packages.[6]
- Research and Development – laboratory buildings including animal labs, storage space, in process labs, QA labs and pilot plants.[6]
- Other – final category dedicated to any area that does not fall into any of the above main categories.[6]

Since data regarding space allocation in the above categories is not collected in the Census of Manufacturers, data had to be provided directly from participating entities within the program.[7] Similar to the commercial buildings program, the pharmaceutical EPI takes several inputs regarding percentage of facility floor space allocated to the above functions, hours of operation, location, and utility costs and in return will provide a 1 to 100 percentile rating for the facility. This tool also now provides the EPA with a benchmarking tool to grant the Energy Star rating to facilities scoring in the 75th percentile or above, which was not previously possible.

Variations in Benchmarking Data

When the EPA initiated discussions about developing a plant level benchmarking tool with pharmaceutical manufacturers, most initial reactions from experts within these companies were skeptical about whether a useful benchmark could be developed. The typical approach for the development of EPI's for other industries is to relate plant input to plant

output as expressed as a unit of production. The pharmaceutical EPI does not. It was decided that the value of product shipments would not provide a uniform measure of activity since, as discussed above, while the level of production is not insignificant, much of the energy use in this industry is devoted to environmental control.[7]

Those involved in the development of the tool self-admittedly state that normalization of all facilities against the three categories allocated may not be entirely appropriate. Specifically recommended in this article is the development of additional categories in accordance with the ISPE Baseline® Guides at a minimum. As a particular example, separate categories should be developed to differentiate the large energy consumption differences that exist between oral solid dose form, aseptic processing, and biopharmaceutical processing. The good engineering practices that govern the design of these types of manufacturing processes are vastly different. Yet, under the current model, these processes are all grouped together.

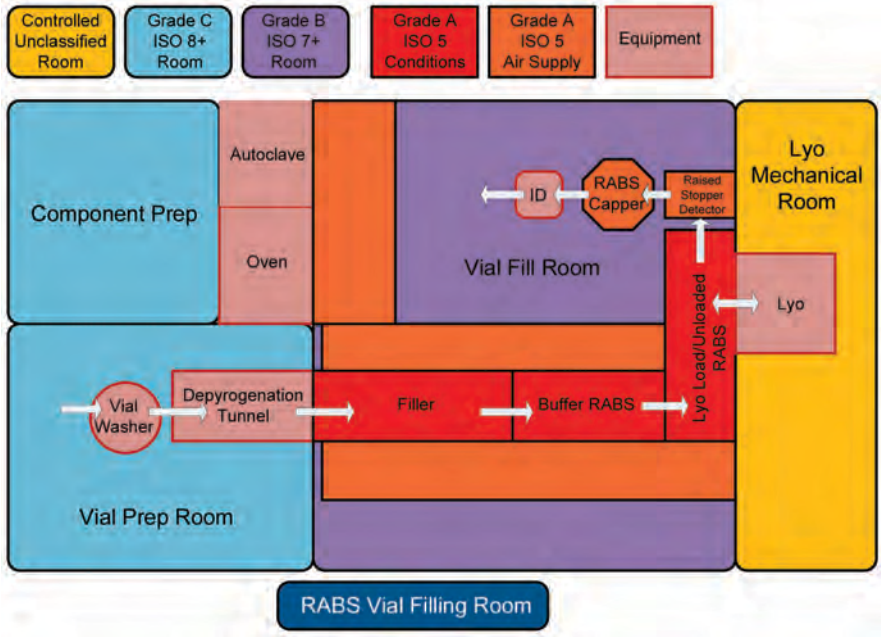

Figure 2. Vial filling suite utilizing a RABS.[8]

Even among the subsets of different aspects of pharmaceutical processing as laid out in the ISPE Baseline® Guides, certain design factors will drastically affect the energy consumption from one facility to the next. For example, cross-contamination concerns at an oral solid dosage facility handling multiple products may encourage the HVAC system designer to utilize 100% outdoor air, whereas a single product facility may utilize a recirculation HVAC system using supplemental filtration to minimize the risk of airborne cross-contamination. The energy consumption impact of 100% once through systems versus a recirculation system can be as much as three times.

Similarly, consider the various cleanroom contamination containment control technologies used in aseptic/sterile processing. Assume the following air change design criteria for this analysis:

- Unidirectional airflow ISO 5 (in operation) / EU Grade A – 300 – 600 ACPH
- Non-unidirectional airflow ISO 7 / EU Grade B – 60 ACPH
- Non-unidirectional airflow ISO 8 / EU Grade C – 30 ACPH
- Non-unidirectional airflow controlled unclassified – 15 ACPH

The design criteria listed above assumes a conventional recirculation type HVAC system with no unoccupied/silent hour airflow or temperature/humidity setbacks. A vial filling suite using a Restricted Access Barrier System (RABS) requires ISO 5 (in operation) (EU Grade A) conditions within the RABS in an ISO 7 (in operation)/ Grade B background as shown in Figure 2.

The same vial filling suite utilizing isolator technology instead of a RABS reduces the suite classification requirement to an ISO 8 (in operation)/ Grade C background (note that EU would allow a Grade D background). In addition, the ISO 5 (in operation) environment is completely contained with the micro-environment within the isolator as seen in Figure 3.

Analysis of the different containment technologies shows a 30-50% energy savings using isolators versus RABS technologies within the HVAC systems serving the filling suites themselves.

Based on the dataset gathered for the pharmaceutical EPI tool, the mean facility is 27% bulk chemical (API and excipient), 20% fill/finish and 10% research and development by space allocation. The remaining 43% is classified in the other designation. The median facility EUI is 1,391 kBtu/sq.ft. (4,391 kWh/m^2) (50th percentile rating). The score needed to qualify for Energy Star (75th percentile) is 806 kBtu/sq.ft. (2,544 kWh/m^2).[4] The main purpose of the examples presented is to show that once the facility is designed, the energy performance is largely locked in and significant variations can exist. Therefore, it comes into question what the benchmarking data is actually showing; is a 75th percentile score depicting the performance of buildings that display significant energy management best practices or is it simply

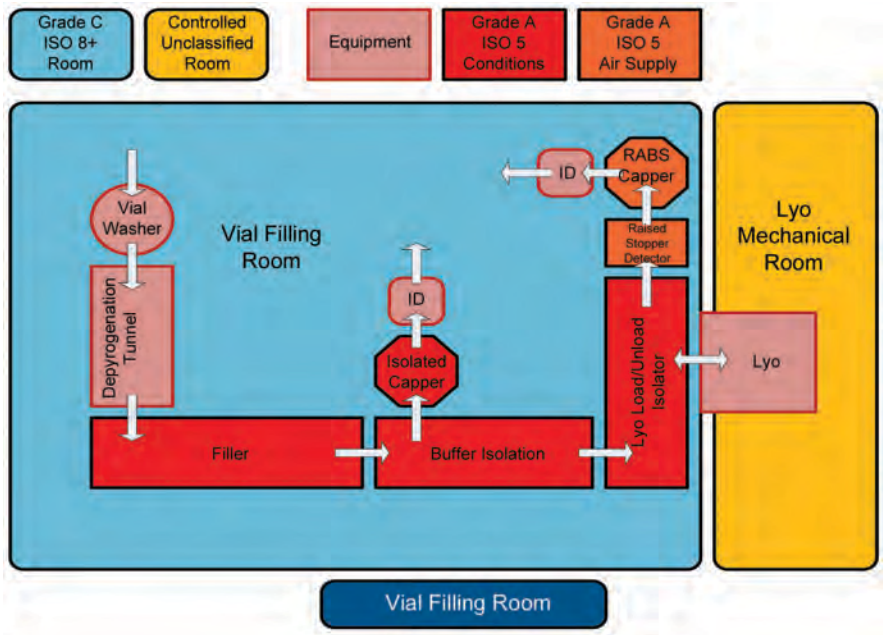

Figure 3. Vial filling suite using isolator technology.[8]

a result of the inherent facility design driven by less stringent process requirements?

Making a Meaningful Impact to Facility Energy Reductions

Perhaps it is best to answer a question with another question; does it matter? While the type of facility being analyzed may be precluded from ultimately achieving an Energy Star certification, the better use of the EPI tool is to use it as a gauge to measure a facility's ongoing energy management strategies over time. A reduction in annual score in an otherwise unchanged building may hint that a tune up is needed via retro-commissioning. The average pharmaceutical facility would need to reduce overall energy consumption by a third to reach the Energy Star threshold; the equivalent of the total EUI of five commercial office buildings of equal size.

While such a task may seem daunting at the onset, most pharmaceutical entities have aggressive internal mandates to reduce energy expenditure year over year. With the current downward pressure on internal costs, a 5% target reduction annually is not uncommon. It is not that many years down the road where the Energy Star certification becomes within reach. However, achieving this lofty annual energy reduction goal goes far beyond conventional energy retrofit projects.

Based on the breakdown of pharmaceutical energy consumption by end use, it can be seen that traditionally common energy retrofits, such as lighting upgrades or motor replacements, do not make a significant impact. Lighting accounts for only 2 to 3% of overall energy usage in pharmaceutical manufacturing, even a 50% reduction in lighting usage will barely yield significant savings as it pertains to overall facility EUI. Lighting retrofits certainly should not be discounted, especially since they are frequently subsidized by utility rebate programs, which enhance the overall project payback. However, in this industry, the energy is tied into the process itself and the supporting systems. For example, reducing the overall ventilation rate by only 5 to 10% in a pharmaceutical facility is the equivalent of eliminating the total lighting energy use in the facility.[9]

Significant reductions cannot be achieved unless the process itself is analyzed, challenged, and optimized. Doing so is a task that requires significant expertise and knowledge regarding the regulatory and cGMP requirements of the manufacturing processes. Maintaining the environment to ensure product integrity and operating personnel protection and comfort are crucial factors that must be accommodated when making any changes to the process to save energy.

Current Industry Trends

In the past, energy expenditures have been a small portion of the total cost of goods in the pharmaceutical industry and thus were not overly a major concern. Over the last decade especially, with increased economic headwinds and rising energy costs, energy consumption is being much more scrutinized. Not only is there the impetus to lower overall internal costs, the industry is pushing toward more environmental stewardship and carbon reduction in light of larger global environmental trends. As a result, energy efficiency is being driven into the technologies used within the industry. For example, isolator technologies currently in production will utilize catalytic converters to break down Vaporous Hydrogen Peroxide (VHP) used during decontamination cycles into non-harmful constituents. This use of catalytic converters speeds up the aeration process and also negates the need for the HVAC system serving the isolator to go into purge mode (100% once through) during aeration.

As the industry moves forward, energy consumption and cost will continue to be under downward pressure. Unless a low cost, clean energy source is developed and industrialized, there is no near term end in sight. Many large pharmaceutical companies have long since implemented energy management programs, albeit to varying degrees of success. The challenge for some is now becoming how to continue to make improvements once all of the quick wins have been

garnered while still remaining fiscally responsible. For others, mainly contract and generic manufacturers, efforts are ramping up to begin to manage and control energy costs. Where normal business practice has always been first cost sensitive, operating costs are quickly rising to the point where they can no longer be ignored.

Conclusion

Normalizing energy consumption across the pharmaceutical industry as a whole has proven difficult. Placing all of the operations that occur within the manufacturing processes into three separate categories for analysis may not always be specific enough for a true apples to apples comparison between facilities. Unlike in the commercial building sector, a pharmaceutical facility meeting the Energy Star performance threshold may have achieved the certification simply as a result of the process requirements driving the design of the facility without any significant introduction of energy management best practices. Similarly, a facility with many energy optimization strategies in place may ultimately be precluded from achieving certification based on the original factors considered during its design. However, benchmarking data using the EPI does prove valuable if the results are interpreted in the proper way and even more so if tracked over time. Using the benchmarking tool to establish baseline energy performance and updating it on a regular basis will allow the user to monitor how well their facility is performing against its own baseline (which is key to validating the efficacy of the overall energy management program). While the energy performance range of a pharmaceutical manufacturing facility is often determined even before the facility is built, through consistent energy management best practices, the facility can certainly optimize the hand it was dealt. This not only is the environmentally responsible thing to do, it is now recognized good business practice.

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Construction Waste Reduction

by Jessica Cochran and Alicia Pandimos Maurer

This case study presents the strategies and outcomes of implementing a plan to divert waste from the landfill and back into the supply chain during construction for building demolition waste reduction.

Innovation in manufacturing often results in the need for new or updated manufacturing facilities. The upfront cost of bringing new products to market also carries hidden environmental costs. The demolition and renovation of these facilities requires the removal of building material that is typically discharged into landfills and carries a serious environmental impact. Construction waste and demolition debris are considered to be industrial waste. Some of this waste is dumped in municipal solid waste landfills along with household garbage, some is incinerated in combustion facilities, but most goes into landfills dedicated to construction waste.[1] While hazardous waste is regulated by the U.S. Environmental Protection Agency (EPA), most construction waste is considered to be non-hazardous and is regulated by individual states, making it difficult to track.[2] Of the estimated 545 million tons of non-hazardous waste managed by the solid waste industry in the US every year, more than half is industrial waste.[3]

Most of this non-hazardous waste that is allowed in landfills can be diverted. Construction waste is deemed to be diverted if directed back into use with little or no modification (materials reuse) or re-directed back into the manufacturing process through recycling (materials are used as raw materials to generate new products).

Recently, Ceva Biomune, CRB Engineers & Builders (CRB), and Demolition Interior Specialists, Inc. (DIS) teamed up to reduce the environmental impact of their project, Project Radical, in Lenexa, KS. Project Radical is a full renovation of an existing warehouse into a 33,000sf, two-story space which includes offices and BSL-2 laboratories. Ceva Biomune's decision to remodel rather than build a new facility not only reduced the amount of building fabric to be disposed of, but was more economical. After researching the local municipality's code requirements and "grandfathering" programs, the design team committed to reusing the existing building. Although the extensive demolition was required to repurpose the building, the design and construction teams were able to divert 90% of the demolition waste, providing a successful case study.

Before a strategy to divert the demolition waste was establish, CRB Builders estimated the demolition would take four weeks to complete. With taking time to salvage, catalogue, and arrange hauling of removed elements, demolition took five weeks. Negative labor cost impacts from extending the schedule by a week were nullified through revenue from selling recycled materials and by reduced landfill tipping fees. Although there is additional work required to use alternative methods of demolition, these efforts not only lowered the cost of demolition, it also reduced the project's environmental impact Unneeded materials were sold to be reused, whether in another project or to be incorporated into a manufacturing process. Items that were not sellable were given to a reuse organization as charitable donations.

All debris removed from the job site was evaluated to fit into three basic categories; reduction, reuse, or recycling. Anything that could not fit into one of those categories was sent to the landfill. DIS compiled and utilized a network of local and national reuse and recycling service providers to cycle material back into the supply chain.

The idea of renovating a building that is at the end of its usefulness is a very sustainable concept in terms of reduction. The more of the existing building that is left intact, the more waste is reduced. Because a wrecking ball was not used during demolition, it was possible to leave major building elements such as the roof and structural steel intact. The simple act of reusing the building itself and maintaining these existing elements created an estimated cost savings of $500,000.

Many building components can be reused in other construction. Architectural items such as cabinets, light fixtures,

hardware, metal stairs and platforms, windows and doors-including frames, if removed carefully, can be reinstalled. The same is true for furniture and some finishing materials, including wood trim and flooring. It is common practice to reuse expensive equipment such as air handler units, compressors, and chillers. However, reuse strategies also can be applied to smaller HVAC, plumbing, and electrical items such as sinks, toilets, faucets, diffusers, junction boxes, outlets, fittings, and valves. With forethought and knowledge of available resources, a new project can be designed to incorporate used or salvaged building elements in the new construction.

With forethought and knowledge of available resources, a new project can be designed to incorporate used or salvaged building elements in the new construction.

Because Project Radical was converting a warehouse into a clean space for laboratories, it was not appropriate to reuse the existing interior elements in the renovation area. Materials identified for potential reuse were sold or donated as architectural salvage to be reused in building projects by schools, religious organizations, and other non-profit programs and charities – both public and private. For example, some items were given to Habitat Restore to be sold to the general public at discounted prices. Donations were documented by affidavit and created positive tax implications for the owner. Other architectural salvage not donated was reserved for personal reuse by the client or project staff. By the end of the demolition phase, 110 cabinets, 100 wooden joist, 49 wooden trusses, 6 chairs, and a water heater had been salvaged and put back into the building supply chain for a total of 23,750 pounds (10,772.8 kg) of diverted waste.

Materials that could be returned to the manufacturing process as raw materials or modified for reuse in other applications were recycled. These items could be separated on-site through waste separation programs, or hauled away from the construction site commingled. The sorting process was primarily done by hand by the demolition company which specializes in construction waste diversion and reuse. 1,132,524 pounds (513,704.2 kg) of concrete were removed from the existing building and sold to a local concrete com-

pany to be crushed and used as aggregate in new concrete. 36,360 pounds (16,492.6 kg) of valuable metals, found in copper piping, steel, and copper wire, were sold to a metal recycling company. 17,720 pounds (8,037.7 kg) of removed wood products were also sold to a recycling company. Typically, gypsum wallboard would be recycled to be introduced back into the production stream or used as a soil conditioner. However, there are currently no companies in Kansas that process gypsum wallboard. The team determined that the environmental and financial benefits would be negated by the embodied energy and cost required to haul the drywall waste to another state for recycling.

In the end, the team's waste reduction strategies paid off. Of the more than 1.3 million pounds (609,916 kg) of construction waste and demolition debris generated during the building of Project Radical, more than 1.2 million pounds (548,981 kg) – more than 90 percent – were diverted from landfills. The steps taken by CRB, DIS, and Ceva, serve as an example of waste reduction management becoming an effective strategy to lower cost and materials while protecting the environment and its natural resources.

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Best Practices in Total Particulate Monitoring in Cleanrooms, RABs, and Isolators

by Members of the Heating, Ventilation, and Air Conditioning (HVAC) and Sustainable Facilities Communities of Practice

This article presents best practices when designing, qualifying, and routinely monitoring for total particulate (viable and non viable) in cleanrooms, Restricted Area Barrier systems (RABs), and manufacturing isolator systems, (excluding sterility testing isolators).

This article describes best practices when designing, qualifying, and routinely monitoring for total particulate (viable and non viable) in cleanrooms, RABs, and manufacturing isolator systems, (excluding sterility testing isolators).

Particulate monitoring is a key parameter for determining adequate control of classified areas, because of its importance, regulatory agencies have clearly stated what the expected specifications for particulates are, based on the classification of the area and the processes being performed within the area. Published studies have shown that there are multiple factors that can negatively affect accurate particulate sampling such as the length of tubing, material of construction of tubing, the velocity of sampling, sampling direction, etc, making it imperative to design the particulate monitoring systems and methods appropriately to demonstrate sustained control.

Background

The regulations require that sterile products be manufactured in areas meeting specified grades of cleanliness (classified areas). In particular, the EU regulations[1] require monitoring of Grade A (ISO 5) areas during critical processing, and recommends a similar approach be used for Grades B through D (ISO 7-8) areas; the FDA guidance[2] has similar classification requirements and recommends routine monitoring (see the Appendix for related regulatory references).Based on these regulations, there are two distinct activities required to show adequate control of classified areas:

1. Initial area classification and periodic requalification
2. Routine monitoring

An integral part of qualification and routine monitoring of classified areas is the particulate monitoring system; this system consists of a sampling probe, sampling tubing and the actual particle measurement device. The accuracy of the particulate data is determined by the extent of particle losses from the sampling probe and the sample tubing; the particle losses are dependent on tubing type, velocity, diameter and distance. The larger particles (e.g., ≥ 5 micron) are lost by a combination of gravitational settling and inertial deposition of the walls of the tubing when directional changes occur. Smaller particles are lost mainly by Brownian motion as well as thermophoretic and diffusion forces.

The length of the sampling tubing should always be minimized to the extent possible without interfering with the manufacturing processes. Some losses are to be expected, but adequate design of a system should minimize this loss. The factors to be considered when designing and operating a particulate monitoring system include:

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- Sample tube material
- Sample tube length
- Number and radii of bends of sample tube
- Flow velocity (diameter of tubing, Reynolds number)
- Sampling probe
- Particulate monitoring equipment, including the use of discreet samplers versus a manifold system.
- Particulate monitoring for isolator/RABs

This article will discuss each factor and recommend a best practice. In addition, it will make recommendations on qualification, requalification, and routine sampling.

Results

The purpose of this article is to address the following points in reference to particulate monitoring:

- To discuss the best practices when designing a total particulate monitoring system
- Clarify requirements for area qualification/ requalification and routine particulate monitoring

Best Practices when Designing a Particulate Monitoring System

Sample tube material should be chosen to avoid electrostatic forces that can cause static build-up of particulates, which may alter the accuracy of the particulate count readings. The ideal tubing materials are listed below in order of preference:

- Purpose made tubing (e.g., co-extruded tubing made of PVC exterior with liner of polyester) is recommended; however, this may not be acceptable in applications where chemical sanitization is carried out.

Other choices are listed below in order of preference:

- Stainless steel – clean and conductive, but expensive and more difficult to install
- Polyurethane – chemically resistant and is lower cost than others.

Other considerations:

- Sample tube cleaning or replacement may be considered to limit the retention of particles on the wall of the sample tubing.
- Tubing material must be resistant to cleaning and sterilization materials/gases likely to come in contact with the tube, this is especially important in isolators where the tube may be exposed, and sanitization may be routinely carried out.

Sample tube length is one of the most important considerations for particulate monitoring. Tubing length should always be kept to the minimum length, keeping the particle monitoring sensor as close as possible to the actual sampling location without interfering with the manufacturing process. Some studies have shown a 5 micron particle loss of less than 20% for 3/8" tubing of 2 meters with a flow rate of 28.3 LPM (1 CFM), and almost 50% for 3 meter tubing at the same sampling rate, showing that larger particles fall out relatively quickly over the length of the tubing - *Figure 1*.

- Maximum length of tube – 10 feet (3.05 meters) or manufacturer's recommendations, if less
- Any tubing length greater than 10 feet (3.05 meters) should have particulate count loss studies included as part of a risk assessment.

Sampling probes play a role in particle loss as well. Factors that can affect particle loss include orientation of the probe; velocity and direction of the air stream; velocity of the sampling flow at the sampling probe inlet; and the geometry and shape of the sampling probe inlet. Isokinetic sampling, which is when the velocity in the supply air is the same as the air

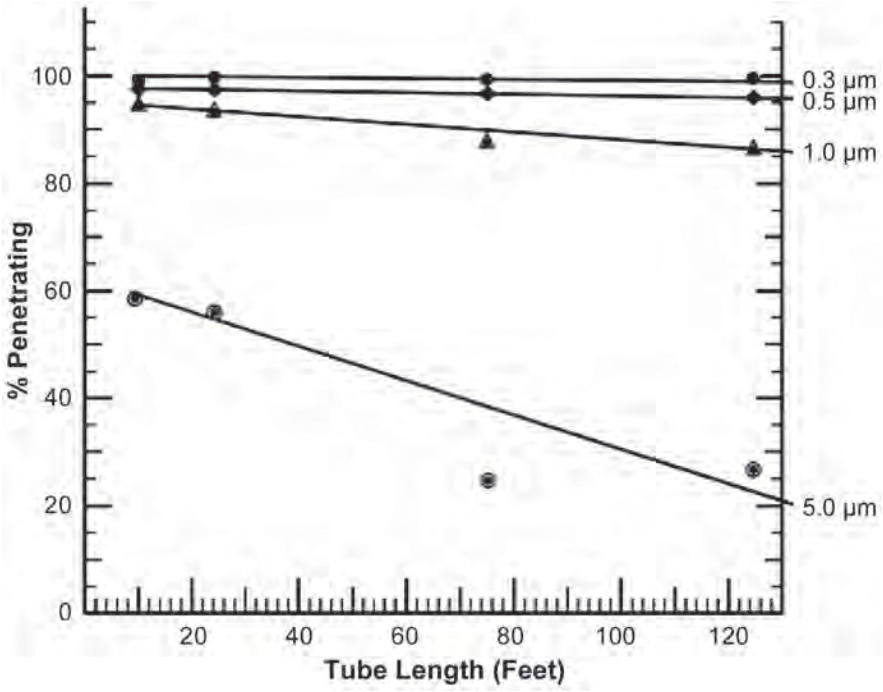
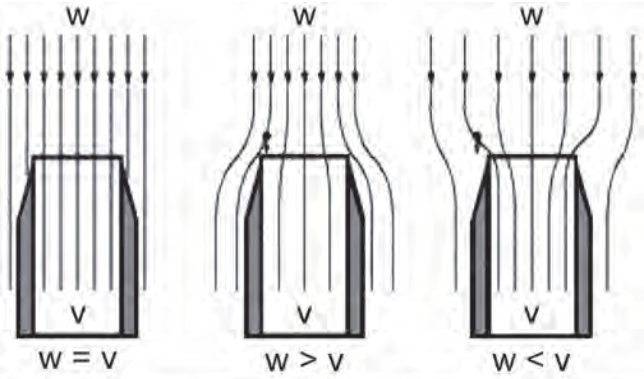


Figure 1. Particle loss based on the size of particle and tubing length (1/2" tubing at 100 liters/minute flow rate).



In the isokinetic case (velocity at w = velocity at v), all particles flowing toward the intake opening are equally collected. If the sample taking velocity is too low (velocity at w > velocity at v), heavy particles can enter the probe even if the flow line on which they were located passes by the probe, causing falsely high readings. If the sample taking velocity is too high (velocity at w < velocity at v), heavy particles fail to adhere to the flow lines and end up by passing the probe, causing false low readings. The error occurring in the case of *under*-isokinetic sampling (center) is many times larger than in the reverse case.

Figure 2. Isokinetic sampling probe.

velocity in the particle monitor's sample-tubing inlet, is necessary when the airflow is unidirectional, such as laminar flow situations - *Figure 2*. If isokinetic sampling does not occur, the data generated will be biased and unreliable, resulting in over-reporting or under-reporting of particulates.

- Thin-walled probes used in unidirectional flow situations should be of isokinetic design and face directly into the airflow (Figure 1).
- If the direction of the airflow being sampled is not controlled or predictable (e.g., non-unidirectional airflow), the inlet of the sampling probe shall be directed vertically upward.
- Samples should be taken at approximately working levels within 12 inches (30 cm) of the operation being monitored, without interfering with the manufacturing process.

Note: an isokinetic probe will be used where tubing is connected to the instrument and it is used for unidirectional flow, for non unidirectional flow a simple tube is sufficient.

Number and radii of bends – the path of airborne particles may deviate from the air streamlines due to their inertia when the direction of sample flow is diverted by a bend. The number of bends must be minimized and the bends should be maintained at the largest possible radius to reduce losses through transportation and to allow for an accurate count.

- Maximum of 2 bends, with the radii radius of curvature not less than 6" (15 cm) - *Figure 3*.
- **Flow velocity** must be sufficient to ensure turbulent flow in the sample tube. Turbulent flow is obtained with a Reynolds[3] number of more than 2500 – the choice of particulate monitoring equipment (and the sample flow rate) and the diameter of tubing should be selected during system design to ensure the Reynolds number is between 3000 and 5500 as seen in Table A. Turbulent or laminar flow is determined by the dimensionless Reynolds Number. The Reynolds number is important in analyzing any type of flow when there is substantial velocity gradient (i.e., shear.) It indicates the relative significance of the viscous effect compared to the inertia effect. The Reynolds number is proportional to inertial force divided by viscous force (the Reynolds number must exceed 3000). The Reynolds number will need to be checked if the flow rate or tube diameter is changed. The Reynolds number range proposed is one for which no significant deposition occurs for particles smaller than 5 to 10 micron size. The residence time in the tubing should be no more than 10 to 20 seconds ensuring transmission of particles larger than 0.1 µm before any significant losses occur. The requirement is to obtain a Reynolds number of 3000 to 5500 when sampling.

Higher flow rate particulate monitoring equipment with the ability to test larger volumes of air (e.g., 50 LPM) may be preferred for cleanroom qualification/requalification.

Particulate monitoring equipment, which takes 1 CFM (28.3 LPM) sample size, may be preferred for routine critical site process monitoring as the cubic meter sample size is not required.

Particulate monitoring equipment should be purchased based on its intended use, for this application:

- Particle monitoring equipment should be designed to detect airborne particles of designated sizes (e.g., ≥0.5, micron ≥ 5 micron) in a cleanroom environment.
- Ideally, individual units should be used in order to reduce the length between sampling and sampling sensors. If a manifold system is in place, studies should be performed

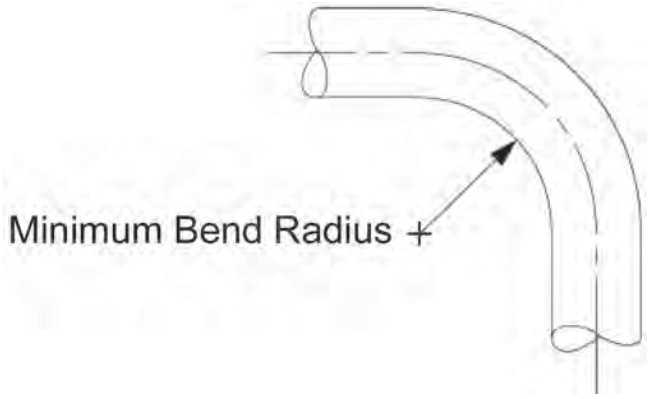


Figure 3. Number and radii of bends.

to ensure that particle loss during sampling is acceptable for the application as compared to the use of discreet sampling units. Particle counters should be calibrated to ISO-21501-4. Some particle counters made prior to 2007 are unlikely to pass this more stringent calibration requirement, check with your equipment supplier.

- If a manifold system is in place, individual tubes should meet the requirements defined above.
- The certificate of calibration of the particle counter should mention the tube length and nature of material (e.g., stainless steel] or polymer).
- When calibration of the particle counter is performed by an external laboratory, the initial readings taken from the system should be compared to the previous readings to ensure that they are within the limits of calibration.
- Where justified by contaminants in the process that would damage the particle counter or present a hazard, (e.g., live organisms, radiological hazards), monitoring during set-up prior to the exposure to risk is acceptable.

Particulate Monitoring for Isolator/RABs may have particular considerations:

- A routine monitoring plan should include the need for sampling in cases where there are intrusions into the system, (e.g., RAB panels be open for adjustments).
- As with monitoring in classic cleanrooms, the length between the sampling probe and the particle sensor shall be as short as possible in order to avoid particle loss.
- When sterilizing/decontaminating units with agents such as Vaporized Hydrogen Peroxide (VHP), ensure the units are not running and the sample point is capped off in order to avoid damaging the equipment with the highly oxidative sterilizing substances.

Requirements for Particulate Monitoring for Area Qualification/Requalification and Routine Monitoring Plans

Regional regulations have slightly different requirements as shown in Tables B and C.[4] The majority of regulations now reference a common ISO Standard (ISO 14644) to define the method to test and demonstrate compliance with the regulations.

Initial Area Classification/Qualification

The initial qualification should include the following as applicable:

- Confirmation that the installation has the correct (specified) grade of HEPA filters (including verification of the certification of the filters).
- Confirmation of a satisfactory leak test of the HEPA filters (to ISO-14644-2 or an acceptable equivalent). Leak testing typically includes confirmation of the air flow rate as well

			28.3 LPM	50 LPM	75 LPM	100LPM	
Tube Bore	Tube Bore (M)	Tube Area M3	Velocity in tube M/S				
1/4"	0.00635	0.00003167	14.89	26.31	39.47	52.63	
3/8"	0.009525	0.00007126	6.62	11.69	17.54	23.39	
1/2"	0.0127	0.00012668	3.72	6.58	9.87	13.16	
			0.000471667	0.000833333	0.00125	0.001666667	Flow volume M3/S
Air Density	1.199	Kg/m3					
Air Viscosity	0.00001837	Kg/m-s					

Reynolds Numbers				
Tube Bore	28.3 LPM	50 LPM	75 LPM	100LPM
1/4"	6173	10906	16359	21811
3/8"	4115	4847	7270	9694
1/2"	3086	2726	4090	5453
Preferred Selection =				

Re = Reynolds Number
D = Tube Inner Diameter (m)
U = Average Fluid Velocity m/s
Q = Sample Flow Rate
ρ = Air Density
μ = Air Viscosity
A = Inner Tube cross sectional area πr2
U = Q/A
Re = DUρ/μ
Standard Figures:
Air Density (ρ) (at 10°C dewpoint, 20°C and 760 mm Hg) = 1.199 kg/m3
Air Viscosity (μ) 0.00001837 kg/m-s

Table A. Reynolds Number Calculation.[3]

as air flow uniformity.
- Air change rates (usually confirmed by the airflow rate verification included in the leak test)
- Airflow visualization
- Room recovery tests. Note: this may be completed during commissioning of a new or refurbished area using particulate generated from a smoke generator, based on the time required to get the log reduction in particle count.
- Area differential pressures

Requalification of Classified Areas

For re-qualification of Grade A areas the following activities should be performed:

- Filter leak test – every six months. Note: testing typically includes confirmation of the air flow rate as well as air flow uniformity, thus confirming air change rate.
- Area classification – every six months
  - Area differential pressures are not required to be checked as they are continually monitored; it would be a good practice to review the area performance and alarms from the monitoring system and include this in the filter test report to ensure that this aspect of the area performance is being maintained.
- For re-qualification of grade B areas, the following activities should be performed:
  - Filter leak test – every six months. Note: testing typically includes confirmation of the air flow rate as well as air flow uniformity, thus confirming air change rate.
  - Area classification – annually
  - Area differential pressures are not required to be checked as they are continually monitored; it would be a good practice to review the area performance and alarms from the monitoring system and include this in the filter test report to ensure that this aspect of the area performance is being maintained.

For re-qualification of grade C areas, the following activities should be performed:

- Filter integrity – every six months (note testing typically includes confirmation of the air flow rate as well as air flow uniformity.)
- Area classification – annually
- Area differential pressures are not required to be checked as they are continually monitored; it would be a good practice to review the area performance and alarms from the monitoring system and include this in the filter test report

to ensure that this aspect of the area performance is being maintained.

For re-qualification of grade D areas, the following activities should be performed as applicable:

- Filter integrity – annually with a visual inspection for damage every six months. Note: testing typically includes confirmation of the air flow rate as well as air flow uniformity.
- Area classification – annually
- Area differential pressures are not required to be checked as they are continually monitored; it would be a good practice to review the area performance and alarms from the monitoring system and include this in the filter test report to ensure that this aspect of the area performance is being maintained.

Airflow Visualization

Airflow visualization tests should be repeated on a regular basis, at least every five years – with the change management process used to determine if it need to be carried out due to changes in the area.

Notes: there should be a definition of the" at rest" and "in operation" states, this may be by area or room contained within an SOP; the definition should include a definition of equipment to be installed and running and the number of operators to be present.

Routine Monitoring

Background: Routine monitoring is used to trend the particulate readings in areas of high risk, particularly during manufacturing and is **not used** to provide confirmation that the area remains within the defined classification limits. Therefore, routine monitoring does not need to be performed according to EN ISO 14644-1, where it specifies using a grid to select sample locations; it can be performed with a reduced number of sampling points and sample volumes based on a formal risk assessment process.

PIC/S guidance suggests:

"Monitoring, on the other hand, does not need to be performed according to EN SO14644-1. It can be performed for a reduced number of sampling points and sampling volumes. A formal risk analysis study based on experiments and analysis of the monitoring data (over at leastsix month operation) should provide a basis for the determination of frequencies and limits. Frequencies and limits should be process based and the results of the initial qualification and ongoing monitoring should be taken into account when setting operational alert and action limits. These limits and sample locations should be periodically reviewed for on-going validity of the risks initially considered.

Those frequencies and limits should be process-based and the results of the qualification should be taken into account.

Reference	Description			Classification				
ISPE Sterile Product Baseline® Guide (Second Edition)	Environmental Classification			Grade 5	Grade 7	Grade 8	Controlled Not Classified (with local monitoring)	Controlled Not Classified (CNC)
European Commission EU GMP, Annex 1, Vol. IV, Manufacture of Sterile Medicinal Products (effective 1 March 2009) (similar to PIC/S GMP Annex 1 2007)	Descriptive Grade			A	B	C	D	Not defined
	At Rest	Maximum no. particles permitted per m^3 ≥ the stated size	0.5 µm	3,520	3,520	352,000	3,520,000	-
			5 µm	20 ("ISO 4.8")	29	2,900	29,000	-
	In Operation	Maximum no. particles permitted per m^3 ≥ the stated size	0.5 µm	3,520	352,000	3,520,000	Not stated	-
			5 µm	20	2,900	29,000	Not stated	-
		Maximum permitted number of viable organisms cfu/m^3		< 1	< 10	< 100	< 200	-
FDA, October 2004, Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm	ISO 5 (Class 100)	ISO 7 (Class 10,000)	ISO 8 (Class 100,000)	Not defined	See ISPE Biopharm Baseline® Guide
		Action level number of viable airborne organisms cfu/m^3		1	10	100	Not defined	-

Table B. Suggested ISPE environmental classifications for aseptic filling and terminal sterilization, including a comparison of US and EU regulatory requirements.

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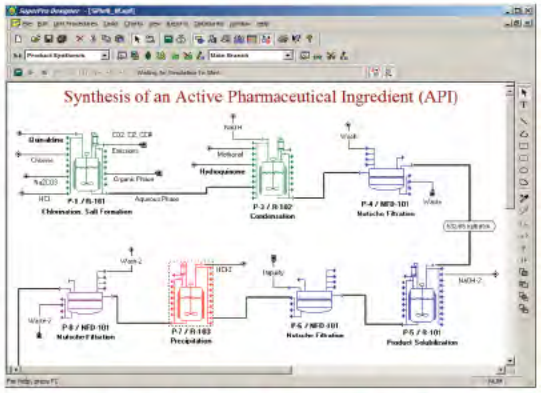

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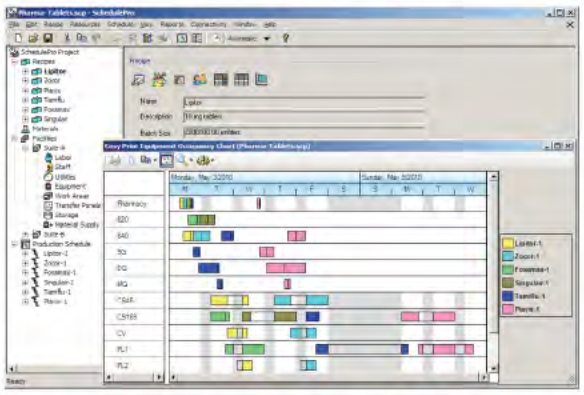

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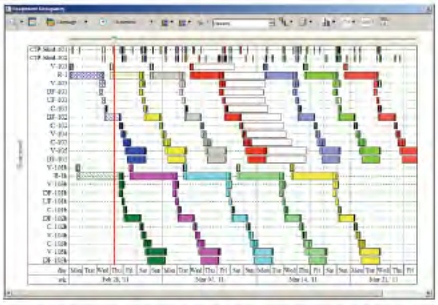

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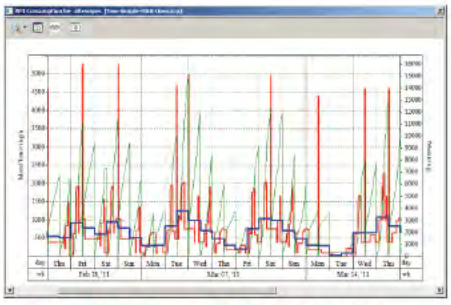
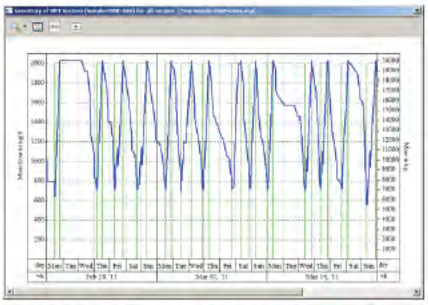


Tracking demand for resources (e.g., labor, materials, utilities, etc.)



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Total Particulate Monitoring

Reference	Description			Classification				
ISPE Sterile Product Baseline® Guide (Second Edition)	Environmental Classification			Grade 5	Grade 7	Grade 8	Controlled Not Classified (with local monitoring)	Controlled Not Classified (CNC)
European Commission EU GMP, Annex 1, Vol. IV, Manufacture of Sterile Medicinal Products (effective 1 March 2009) (similar to PIC/S GMP Annex 1 2007)	Descriptive Grade			A (Note 1)	B	C	D	Not defined
	At Rest	Maximum no. particles permitted per m^3 ≥ the stated size	0.5 µm	3,520	3,520	352,000	3,520,000	-
			5 µm	20	29	2,900	29,000	-
	In Operation	Maximum no. particles permitted per m^3 ≥ the stated size	0.5 µm	3,520	352,000	3,520,000	Not stated	-
			5 µm	20	2,900	29,000	Not stated	-
		Maximum permitted number of viable organisms cfu/m^3		< 1	10	100	200	-
		Maximum permitted number of viable organisms cfu/90 mm settle plate/4 hour exposure		< 1	5	50	100	-
FDA, October 2004, Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing	In Operation	Maximum no. particles permitted ≥ the stated size	0.5 µm	ISO 5 (Class 100)	ISO 7 (Class 10,000)	ISO 8 (Class 100,000)	-	-
		Action level number of viable airborne organisms cfu/m^3		1	10	100	-	-
		Action level number of viable organisms 90 mm settle plates per 4 hours		< 1	5	50	-	-
ISO 13408-1:1998 Aseptic Processing of Healthcare Products (Note 2)	Descriptive Name			Critical Process Zones	Other Process Zones	Non-sterile Support Areas	Not defined	Not defined
	In Operation	Maximum no. particles permitted per m^3 ≥ the stated size	0.5 µm	3,500	350,000	3,500,000	-	-
The following cleanroom standards are also referred to, using the nearest equivalent class at ≥ the stated particle size.								
EN/ISO 14644-1:1999 (Note 1)	In Operation	Class ≥ the stated size (max number of particles at the class limit per m^3)	0.5 µm	ISO 5	ISO 7	ISO 8	Unclass	Unclass
	At Rest		0.5 µm	ISO 5	ISO 5	ISO 7	ISO 8	Unclass
US Fed. Std. 209E (Metric):1992 [Now suspended] (Note 2)	In Operation	Class ≥ the stated size (max number of particles at the class limit per m^3)	0.5 µm	M 3.5	M 5.5	M 6.5	Unclass	Unclass
	At Rest		0.5 µm	M 3.5	M 3.5	M 5.5	M 6.5	Unclass
US Fed. Std. 209E (Metric):1992 [Now suspended] (Note 1)	In Operation	Class ≥ the stated size (max number of particles at the class limit per ft^3)	0.5 µm	100	10,000	100,000	Unclass	Unclass
	At Rest		0.5 µm	100	100	10,000	100,000	Unclass

Notes:
1. There is no specification given in this standard for microbiological limits.
2. On 29 November 2001, Federal Standard 209E dated 11 September 1992 was cancelled and superseded by two international standards published by ISO. These standards are: ISO 14644-1:1999 and ISO 14644-2:2000.

Table C. Comparison of regulatory documents and international standards with the ISPE Sterile Baseline® Guide in regard to classifications for airborne environmental cleanliness requirements.

In critical areas with exposed product continuous monitoring, covering the duration of the operations is expected. Continuous means that the system must be able to pick up any potentially occurring event of an unusual number of particles, including an event that occurs for a short time only. Manifold systems might not be suitable for Grade A Zone monitoring due to a lack in responsiveness. It is important that monitoring in grade A comprises equipment assembly, because there is a high impact of the human operator. An SOP should be present defining alert levels and pre-defined corrective measures in cases of alerts and interventions."

The sample locations should be selected based on a risk assessment; the process flow should be mapped for each of the stages during operation:

- System not in use
- System set up
- Start up
- Normal operation – include normal activities/interventions required
- Emergency stop
- Shut down
- CIP/SIP

Appendix: Related Regulatory Citations

Cleanroom areas for the manufacture of sterile products should be classified (ISO 5, 6, 7, 8, 9) according to the required characteristics of the environment. Each manufacturing operation must had an appropriate environmental cleanliness levels in the operational state in order to minimize the risks of particulate or microbial contamination.[1] (Eudralex Volume 4, Annex 1 General section 3; 21 CFR 2.11 42(10)(v) & 46(b)).

Cleanroom design and clean air device classification are based on particle levels. Cleanrooms and clean air devices are to be classified in accordance with the methods described in ISO 14644-1. The minimum sample volume for classification must be 1 m.[1] (Eudralex Volume 4, Annex 1 General Section 4, 5, 6, 7).

For Grade A zones, particle monitoring must be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, (e.g., live organisms and radiological hazards). In such cases, monitoring during routine equipment set up operations should be undertaken prior to exposure to the risk.

The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, transient events, and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of ≥ 5.0 µm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.[1] (Eudralex Volume 4, Annex 1, General Section 9).

Air in the immediate proximity of exposed sterilized containers/closures and filling/closing operations would be of appropriate particle quality when it has a per-cubic-meter particle count of no more than 3520 in a size range of 0.5 µm and larger when counted at representative locations normally not more than 1 foot from the work site, within the airflow, and during filling/closing operations. This level of air cleanliness is also known as Class 100 (ISO 5).[5] (FDA Guidance for Industry, Sterile Drug Products Proceeded by Aseptic Processing – CGMP, section IV.A).

Monitoring with sampling probes located in such a way that they monitor the air from the HEPA filter rather than the air immediately surrounding the critical zones should be avoided; however, the location of the sample device should not compromise the laminarity of the air flow in the critical zone. Initial validation should be checked to confirm the worst case positions have been adequately identified. These may be confirmed during process simulation tests.[6] (PICS P1 007-5 Recommendation of the Validation of Aseptic Processes, Section 7.2.1).

Grade B zones must be monitored similarly to the grade A area although the sample frequency may be decreased. The importance of the particle monitoring system should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones.[1] (Eudralex Volume 4, Annex 1, General Section 10).

The particulate conditions for the "at rest" state must be achieved in the unmanned state after a short "clean up" period of 15-20 minutes (guidance value) after completion of operations. The recovery test is performed to determine the ability of the system to eliminate airborne particles.[1] (Eudralex Volume 4, Annex 1 General Section 5, ISO 14644-3).

Written procedures must be in place and include a list of locations to be sampled for routine batch related processing. Selection of sampling location consideration should be given to the points of contamination risk in a process including factors such as:

- Difficulty of setup and impact of interventions
- Length of processing time
- Sample timing and frequency
- Duration of sampling, sample size

The monitoring program must cover all batch related production shifts at a defined frequency when materials are in the area, processing activities are ongoing, and a full complement of operating personnel are in the operating area.[5] (FDA Guidance for Industry, Sterile Drug Products Proceeded by Aseptic Processing – CGMP, section X.A., USP <1116>).

Measurements must be taken to confirm air cleanliness in critical areas at sites where there is most potential risk to the exposed sterilized product, containers, and closures.5 (FDA Guidance for Industry, Sterile Drug Products Proceeded by Aseptic Processing – CGMP, section X.A.1).

An environmental monitoring program should be established that routinely ensures acceptable microbiological quality of air, surfaces, and gloves (or half-suits) as well as particle levels, within the isolator. Air quality should be monitored periodically during each shift. For example, monitoring the exit port for particles to detect any unusual particle counts.[5] (FDA Guidance for Industry, Sterile Drug Products Proceeded by Aseptic Processing – CGMP, appendix 1, section F, USP <1116>).

Remote sampling systems should be used in lieu of personnel intervention. Once the validation establishes the effectiveness of the barrier system, the frequency of sampling to monitor the microbiological status can be established based on validation data.[5] (USP <1116>).

Portable particle counters with a short length of sample tubing must be used for classification purposes because of the relatively higher rate of precipitation of particles ≥5.0µm in remote sampling systems with long lengths of tubing. Isokinetic sample heads shall be used in unidirectional airflow systems. The sampling probe must be positioned pointing into the airflow. If the direction of the airflow being sampled is not controlled or predictable (e.g., non-unidirectional airflow), the inlet of the sampling probe shall be directed vertically upward.[1] (Eudralex Volume 4, Annex 1, General Section 6, ISO 14644-IB 4.3.2).

Conclusions and Recommendations

This article has been created to provide guidance on the best practices for the design and installation of total particle monitoring systems to be used for monitoring of production areas.

The two Communities of Practice are working on the development of knowledge briefs that provide information on best practices – if you are interested in contributing, please contact the Chair or Co-Chairs of the COPs for more information:

- Nick Haycocks, HVAC Chair, email: haycocks@amgen.com
- Robert Bowen, HVAC Co-Chair, email: rob.bowen@facilitiesintegration.com
- Gary Knight, HVAC Co-chair, email: gary.knight@cagents.com

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Quantifying Green Manufacturing: An Environmental Assessment Primer from LEED to Benchmarking

by Kacy Wander

This article presents an introduction to corporate sustainability policy and compares several international building assessment systems and emissions reporting practices.

Certified buildings or carbon neutrality? Recycling program or green procurement policy? In a global market where each county seems to have its own building rating system and each corporation reports different environmental data, the options seem overwhelming. To develop a corporate sustainability policy may seem daunting, especially for a pharmaceutical corporation depending greatly on energy and natural resources. Fortunately, the evolving state of global sustainability policy leaves opportunities to innovate and advantages that can ring true with consumers and investors. This article will look at the questions that may arise, and the available options for a global pharmaceutical corporation to develop its sustainability policy.

Creating a Global Sustainability Policy

Simply demanding "BREEAM Excellent" or "LEED Gold" may not suffice for corporations with facilities in multiple countries or continents. It's difficult for the public to compare a "four star" rated facility under the Australian Green Star system to a CASBEE "Class S" building in Japan, yet choosing a single system could prove more challenging to execute in some countries than in others. Fortunately, a few systems are now available internationally, offering somewhat portable options for multinational companies. These include the US-based Leadership in Energy and Environmental Design (LEED) and UK-based Building Research Establishment Environmental Assessment Method (BREEAM). However, the international implementation of these programs can be challenging outside of their parent countries. LEED, for example, awards credits for compliance with several

Figure 1. The availability of building assessment systems can seem overwhelming.

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Carbon (a)							
Type	Unit	2007	2008	2009	2010	2011	2012
Total Carbon Combustion On-site (Scope 1) (f)	1,000 MT CO_2 Eq	126	113	115	114	104	98
Natural Gas	1,000 MT CO_2 Eq	104	92	89	86	74	70
Diesel	1,000 MT CO_2 Eq	22	21	26	27	30	27
Propane	1,000 MT CO_2 Eq	-	0.04	0.16	0.68	0.60	0.63
Total Carbon Purchased Energy (Scope 2) (g)	1,000 MT CO_2 Eq	290	278	296	294	277	287
Electricity	1,000 MT CO_2 Eq	284	272	291	289	273	283
Steam	1,000 MT CO_2 Eq	6	6	5	5	4	4
Total Carbon From Energy	1,000 MT CO_2 Eq	416	391	412	407	381	385
Total Carbon Normalized to Net Sales	1,000 MT CO_2 Eq / $B net sales	29.1	26.6	28.7	27.8	24.9	23.1
Total Carbon Normalized to Total Energy	$MTCO_2Eq$ / GJ	0.095	0.097	0.102	0.104	0.098	0.100
Confirmed Results of CO_2 Reduction Projects (b,c)	1,000 MT CO_2 Eq	0	19	36	49	63	83

Table A. Amgen's voluntary reporting shows a trend of reduced carbon emissions (reproduced with permission, from Amgen 2012 Sustainability Report[3]).

US-based standards, such as Energy Star and South Coast Air Quality Management District, while the new BREEAM International 2013 is not yet available for all project types. Despite the challenges, several international companies are committing to these assessment systems. Johnson & Johnson holds LEED-certified facilities in six countries and three continents,[1] while Becton Dickinson's stock of 12 certified facilities spans three continents.[2]

Prescribed Rating System or Building Performance Goals?

Designing to a rating system may lead companies away from some of the most project-specific sustainable measures. Although several sub-systems based on building type are available, pharmaceutical facilities are difficult to typecast, often being some combination of lab, factory, warehouse, or office. On the other hand, internally created performance goals could be harder for the public to understand than LEED certification, but these internal goals may correspond more directly to company-specific requirements.

Although some rating systems, such as BREEAM In-Use and LEED for Existing Buildings, have provisions for ongoing building operations, most tend to focus on initial design and first-cost items. This can miss opportunities to encourage sustainable operational policies such as cleaning, product packaging, and waste management. For pharmaceutical facilities where such ongoing operations are critical, these shouldn't be overlooked. Companies such as Amgen, GlaxoSmithKline, and Johnson & Johnson, all of which feature LEED-certified facilities, also publish company-specific sustainability goals and annual performance reports. This

Figure 2. Employees feel productive at the LEED Platinum-Certified Genzyme Center in Cambridge, MA (photo source: Peter J.B. Teague).

practice of benchmarking, although it is becoming mandatory in certain locations, is still widely voluntary. Simply tracking energy usage per square foot, which is now law in seven US cities and two states,[3] or reporting annual emissions and trading per the existing European Union requirements and a recent pilot system in China,[4] may be insufficient. To track complex data such as energy recovery, recycling programs, and progress toward internal goals, corporations may follow Europe's recommended format, the International Organization for Standardization (ISO) reporting guidelines,[5] and determine if additional data and formats are needed to communicate achievements to stakeholders. Amgen addresses these complexities by publishing a multi-year report on energy and water usage, carbon emissions, and waste stream information. The figures demonstrate to consumers the trend of reduced carbon emissions since 2007[6] - *Table A.*

For companies with increasing production, it can be helpful to show the ratio of emissions compared to revenue, or to a given unit of product. Johnson & Johnson's annual reporting format shows a ratio of emissions to US Dollars in sales.[7] This comparison, which the US EPA deems *emission intensity*, along with the similar ratio *energy intensity* (energy used to revenue gained), can account for corporate growth while demonstrating a decreasing relative environmental demand.

Pharmaceutical Practice	Rating System Feasibility	Comments
Water		
Water Monitoring	Advantage	BREEAM currently rewards facilities for this practice; LEED v4 (available November 2013) will do the same.
Energy		
Systems Commissioning	Advantage	Both LEED and BREEAM reward projects for sophisticated testing and oversight of the building's systems.
Exclusion of Process Equipment from Regulated Loads	Advantage	Energy models are not penalized for heavy process loads, however this is a missed opportunity to innovate.
Energy Monitoring	Advantage	The common pharmaceutical practice of monitoring energy use or installing submeters is rewarded as a sustainable practice.
Materials		
Low Use of Wood	Advantage	Both LEED and BREEAM reward projects using sustainably harvested wood, as a percentage of total project wood. Projects with little wood have a smaller threshold to meet.
Indoor Health		
High Airflow Rates	Advantage	Although this poses a difficulty for energy credits, the amount of clean air being delivered to spaces can score points for air quality.
High-Performance Air Filtration	Advantage	Air filtration standards for manufacturing spaces often exceed those required by rating systems.
High-Performance Paints and Coatings	Difficulty	GMP facilities often require high-performance coatings: conductive , non-corrosive primers, etc, which often exceed allowable VOC content. Consider a materials procurement policy that limits VOCs.
Constant Lighting at Process Areas	Difficulty	Rating systems prefer occupancy sensors and user-controlled lighting.
Few Exterior Windows	Difficulty	Fewer opportunities to provide natural light and ventilation.

Table B. Comparison of common manufacturing practices to rating system advantages and disadvantages.

What Are the Benefits of Rating our Facilities?

In addition to the obvious benefits of environmental stewardship, quantifying facilities' sustainable design measures is useful for both public relations and as a form of accountability. As assessment is still voluntary, it distinguishes participants as leaders in the industry. Rating systems such as BREEAM and LEED can encourage design innovation, and hopefully will encourage additional process innovation as these systems evolve. They are also associated with operational cost reduction, such as the annual $482,000 in savings that Becton Dickinson attributes to its LEED-certified facilities.[2] Increased employee productivity and satisfaction are also associated with rated facilities, as 72% of surveyed users in the LEED Platinum-certified Genzyme Center reported feeling more alert and productive than in their previous workplace[8] as seen in Figure 2.

Which Rating System is Best?

Many rating systems offer cumulative points from which teams may choose the most feasible measures for the project. To become certified, projects must meet several mandatory standards, plus accumulate elective points from both quantitative and qualitative categories including site design, water and energy efficiency, material sourcing, waste minimization, and indoor comfort. An early adopter of the point-based system was BREEAM, developed in 1990 by the Building Research Establishment. Origi-

nally developed as a UK government agency, BRE is now a private agency offering BREEAM on an international scale, ranking projects from "Pass" to "Outstanding." LEED, developed by the private, non-profit US Green Building Council, is also globally available, while the green building councils of India and Canada have established separate LEED rating systems. In addition to its most popular "New Construction" rating system, LEED offers several sub-systems for unique project types, and it rates projects from "Certified" to "Platinum." Another point-based system is Green Star, which has versions available in both Australia and South Africa. A major advantage of these point-based systems is the ability to select the most advantageous credits, abandoning those that would be more costly or difficult. For a company that is confident about sustainable pursuits in one area, but still developing another, this is an important consideration.

A few green building evaluation systems aim at being a comprehensive design tool rather than a system of points. A newcomer to the global assessment market is Japan's Comprehensive Assessment System for Built Environment Efficiency (CASBEE). This spreadsheet-based tool produces a holistic score, which is the ratio of "quality," or the building's environmental and functional benefits, over "load," or its environmental demands. This ratio "Q/L" results in a sustainability rating ranging from "Class C" (poor) to "Class S" (excellent). Like its point-based counterparts, CASBEE takes into account criteria such as site and indoor environment quality (contributing to Q), and energy and resource efficiency (mitigating L). Pharmaceutical facilities, which often optimize equipment and resource efficiency, may be at an advantage by minimizing loads and contributing to a desirable ratio.

Although these rating systems feature differences in documentation processes, schedules, and most confusingly, rating terminology ranging from a jumble of letters and numbers to various symbols, they all reward similar design measures. Many good management practices that have long been commonplace in pharmaceutical manufacturing are rewarded as environmentally sustainable measures. Practices such as high-performance air filtration, energy monitoring, and systems commissioning are rewarded by both LEED and BREEAM. Another rating system advantage, although a missed opportunity to innovate, is the fact that the energy modeling credits typically consider a facility's process equipment to be an "unregulated load." This allows companies to avoid penalties for having heavy equipment loads, yet it provides no incentive for equipment vendors to improve their products' efficiencies and contribute to long-term savings. Table B compares common manufacturing practices with the advantages and difficulties of common rating systems.

The attainment of certification is becoming additionally feasible as contractors gain familiarity with requirements. Turner Construction reports no additional construction costs for the LEED component of a 345,000-square foot pharmaceutical manufacturing facility, which was recently awarded Gold certification. Project manager David Watts attributes the savings to the increased familiarity of Turner's team and vendors with sustainable practices such as materials reporting, construction waste recycling, and erosion control.[9] For some contractors, these procedures are becoming commonplace.

Conclusion

Should corporate policies demand a building assessment system or create custom protocol? Because pharmaceutical manufacturing relies on both its facilities and ongoing resource management, perhaps both measures are important. As was previously noted, many of the functions of pharmaceutical facilities already lend themselves to high environmental ratings. With most assessment systems offering similar credits, corporations should compare them by geographic availability, public appeal, and assessment time and fees. Once a system is chosen, consider screening design teams and contractors for familiarity with the chosen assessment system. Additionally, examine the company's cleaning, recycling, and materials procurement policies for potential alignments with rating system requirements. In order to eliminate redundant paperwork, it also may be helpful to review corporate utility monitoring and systems commissioning protocol; it may be possible to identify a reporting format that satisfies not only the rating system, but also internal or legislated requirements.

Accountability to rating systems begins to drop off as soon as construction is complete, yet much of the industry's environmental demand occurs after facilities are occupied. Although legislated benchmarking is lagging behind the voluntary efforts of many pharmaceutical leaders, corporations with interests in ongoing energy, emissions, and waste streams may consider self-reporting these data. The global pharma industry has a stake in many countries whose legislation, for better or for worse, is often shaped by the behavior of corporations. This makes it even more critical to lead the way with sophisticated benchmarking and voluntary environmental assessment.

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Alternative Dechlorination Methods in Reverse Osmosis (RO) Applications

by Mark Wilf, PhD

This article examines the effects of different methods of water dechlorination on prolonging the lifespan of RO membranes used for industrial water treatment.

RO Membranes and Applications

Reverse osmosis (RO) technology is the most common method of desalination of high salinity water for potable use and salinity reduction of any water source for production of very low salinity water for industrial applications. The separation of water and dissolved ions in the feed stream is provided by membrane elements.

RO Membranes and Elements

The commercial RO membranes are configured as aggregate composite flat sheet layers of polyester support fabric, polysulfone porous layer, and aromatic polyamide barrier. This is commonly known as Thin-Film Composite (TFC) membranes. The total thickness of composite flat sheet membrane is about 0.2 mm. The polyamide barrier is only 1000 – 2000 angstrom thick. This ultrathin barrier provides the rejection property of the membranes towards the dissolved ions and organic constituents.

The membrane elements are manufactured in a spiral wound configuration. In this configuration, membrane envelopes are connected to a central permeate tube. The number of envelopes in an element depends on element diameter. It is 4 – 5 envelopes for a 100 mm diameter and 20 – 30 envelopes for a 200 mm diameter element. Accordingly, the membrane area of a 100 mm diameter element is 8 – 10 m2, and a 200 diameter element contains 35 – 40 m2 of membrane area.

During the RO separation process, feed water under pressure flushes the membrane envelopes. A fraction of feed water passes the membrane barrier, and as a permeate water flows inside the envelopes to the central permeate tube. Almost all the dissolved ions in the feed water are rejected by the polyamide membrane barrier. The remaining, more concentrated feed water, flows to the next membrane element, connected in series, where additional conversion of feed to the permeate takes place - *Figure 1*.

The composite membrane has very high mechanical and chemical durability. Properly operated, membrane elements can provide stable performance for 3 to 10 years.

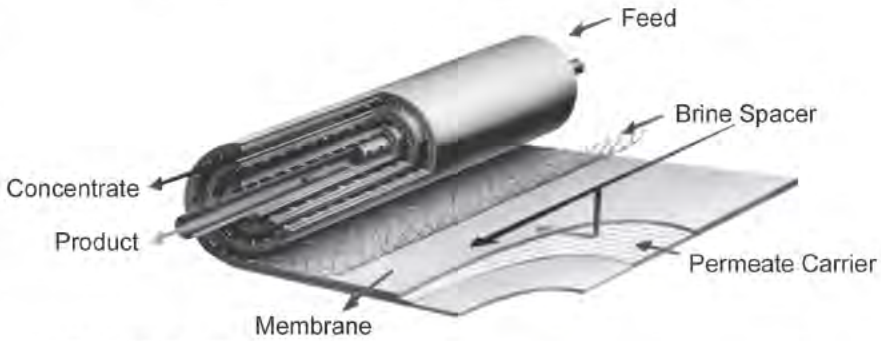

Figure 1. RO spiral membrane design.

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Process Parameters and Performance Indicators of RO Membranes and Membrane Units

The basic process parameters of the membrane unit are permeate capacity (Qp) and recovery rate (R). The recovery rate is defined as a fraction of feed water (Qf) converted to permeate (Qp).

$$R = 100\% * Qp/Qf \quad (1)$$

The permeate capacity is defined by membrane area installed in membrane unit and the designed rate of average permeate flux (l/m2/hr). The flux rate is defined as permeate flow (Qp) produced from a unit area of membrane (MA):

$$Flux = Qp/MA \quad (2)$$

The feed pressure required to produce given permeate flow is a function of average osmotic pressure of the feed water and water permeability of the membrane. Salinity of permeate produced in the membrane unit is a function of average feed salinity and salt rejection of the membrane (SR). Salt rejection is derived from calculation of salt passage (SP):

$$SR = 100\% - SP \quad (3)$$

$$SP = 100\% *Cp/Caf \quad (4)$$

Where Cp is salinity of permeate water, and Caf is average salinity of feed – concentrate stream. During the field operation of RO unit, it is simpler to measure conductivities of feed and permeate streams, rather than conduct analytical determination of concentrations of water samples.

The conversion factor from conductivity to salinity is usually determined experimentally from analytical results of concentration and measured conductivity of water samples. For low salinity waters (concentration below ~1000 mg/l), the value of conversion factor from conductivity to salinity is about 0.50 – 0.55.

The stability of key membrane performance parameters: water permeability and salt rejection uniquely defines the stability of performance of the membrane unit: operating feed pressure and salinity of permeate produced. Conversely, at constant process parameters, the values of feed pressure and permeate salinity provide clear indication about condition of the membranes operating in the membrane unit.

Stability of both membrane performance parameters: water permeability and salt rejection are very important in operation of RO membrane desalination systems. In case of some decline of membrane water permeability, the decline can be compensated by increase of the feed pressure; however, there is no practical solution to correct decline of membrane salt rejection (increase of salt passage). Even a small reduction of salt rejection could result in a significant increase of permeate salinity. For example, reduction of membrane salt rejection from 99% to 98% will result in doubling of permeate salinity, an increase of 100%. Therefore, stability of the salt rejection property of the membrane uniquely defines longevity of membrane elements operating in the desalination unit.

The stability of the salt rejection property of an RO membrane is related to the integrity of the polyamide membrane bar-

Test conditions	Results	Reference No
Free chlorine concentration range ~4000 ppm, pH range 8.5 – 12.5, exposure time 15 – 45 min	Membrane sensitivity to chlorine is pH dependant. Most model compounds are more reactive at low pH	3
Chlorine dioxide concentration range 1, 5 and 10 ppm, pH range 7 – 8.5, exposure time up to 200 days, separate test at pH = 3.5, chlorine dioxide concentration of ~3.8 ppm	Membrane sensitivity to chlorine dioxide is quite similar in the whole pH range of 7 – 8.5. At pH 3.8 performance stable for a test period of 100 days.	4
Free chlorine concentration range 5 - 500 ppm, pH range 4 and 9, exposure time 1 – 360 hr	At low pH = 4 and low free chlorine concentration, only small changes of membrane polymer. High chlorine concentration accelerates degradation. At pH = 9 the degradation process slows down	7
Chlorine, bromine and monochloramines total concentration range 4 – 120 ppm, pH = 8.2, exposure time up to 1,800 min.	Free bromine species damage polyamide membranes at faster rate than free chlorine and chloramines	10
Chlorine concentration range 100 – 3,000 ppm, pH range 3.6 – 10.2 exposure time 1 – 20 hr	Higher degradation rate at lower pH	8
Free chlorine concentration range ~ 30 ppm, pH range 3.0 – 8.6 exposure time up to 328 hr	Sustainable salt rejection and flux at pH 3.0 and 5.8. Some degradation at pH = 8.6	8
Low pH	Membrane more sensitive to chlorine oxidation	16
Characterization of performance of aromatic polyamide membranes. Free chlorine concentration ~ 3ppm	Free chlorine attack is most rapid at low salinity of feed water and high feed water pH	17

Table A. Summary of literature review on chlorination exposure tests.

rier. The membrane barrier could be damaged by mechanical abrasion by suspended particles present in the feed stream or by chemical reaction with chemicals that are not compatible with polyamide polymer.

Effect of Strong Oxidants on Performance of RO Membranes

Among the few chemicals that react with the polyamide barrier and damage the salt rejection property are strong oxidation agents. These include hydrogen peroxide, potassium permanganate, chloramines, and free chlorine. The last two chemicals listed are most frequently present in potable water supply systems.

The assumed process of reaction of free chlorine with polyamide polymer[2] is schematically shown on Figure 1. The chlorine attack starts with chlorination of amidic nitrogen following chlorination of aromatic ring through intermolecular rearrangement.

The assumption is that the first step can be reversed in some conditions. The second step is irreversible and leads to cleavage of the amine bond[5] and damage to the polyamide membrane barrier.

Although there is general agreement that the exposure to free chlorine is detrimental to the salt separation properties of polyamide membranes, the mechanism of chlorination reaction, conditions of the reaction and its kinetics are still not well defined. The information reported in scientific literature regarding parameters affecting chlorine – polyamide membrane interaction is not always consistent, as illustrated in results shown in Table A.

One possible reason for some level of discrepancy between results obtained at different sites is the catalytic effect of a low concentration of transition metals often present in the feed water stream. It has been observed that minute concentrations of iron (Fe) or copper (Cu) in the feed water increases speed of deterioration of salt rejection, even with a relatively low concentration of free chlorine or chloramines present in the feed stream.[4]

Tests conducted in controlled conditions indicated that polyamide membrane has some tolerance to the presence of chlorine in the feed water. The level of tolerance is defined by ppm – hr. The concept of "ppm per hr" is described as a multiplier of concentration of chlorine in ppm multiplied by the exposure time in hours.[6]

The majority of manufactures of composite polyamide

membranes provide a level of membrane tolerance to free chlorine exposure in the range of 1000 – 2000 ppm per hr. However, this limit is very loosely defined, without indication of under what conditions this limit applies. Neither are actual changes of salt rejection specifically defined.

The concept of "ppm per hour" is just a qualitative indicator of membrane performance stability. Accordingly, operational experience shows that accidental, short term exposure of polyamide membranes to free chlorine will not result in irreversible membrane damage which would lead to a loss of salt rejection.[6-7]

Continuous exposure to free chlorine, both water permeability and salt transport through the membrane increases. According to some sources[6] the rate of chlorine attack is higher at higher pH; however, contradictory observations are also reported - *Table A*.

Temperature affects the rate of membrane chlorination in the same way as it affects other chemical processes. The rate increases with temperature. Commercial RO membranes have nominal salt rejection of above 99% – usually 99.5% – 99.6%. Correspondingly, the nominal salt passage is about 0.5%. Any increase in salt passage will result in a significant increase in permeate water salinity.

For example, the reduction of nominal salt rejection from 99.5% to 99.0% will result in an increase of permeate salinity by 100%. Such an increase would usually not be acceptable in the majority of RO applications.

Figure 2 shows the results of a membrane-damage test conducted during August 2011 at Atlantium Laboratories. The shown fitted (and hence "clean") curves indicate the salt passage as determined for two (initially) similar membranes. The free chlorine concentration in the upstream water averaged 1.0 ppm. The free chlorine concentration in the feed water for the protected membrane measured 0.0 ppm ("below detectable level"), while the average free chlorine concentration in the feed water for the unprotected membrane remained unchanged at 1.0 ppm. As shown, the unprotected membrane degraded unusually fast so that within only nine days or so, salt passage doubled. The quick rise in salt passage validates the need for adequate and continuous membrane protection.

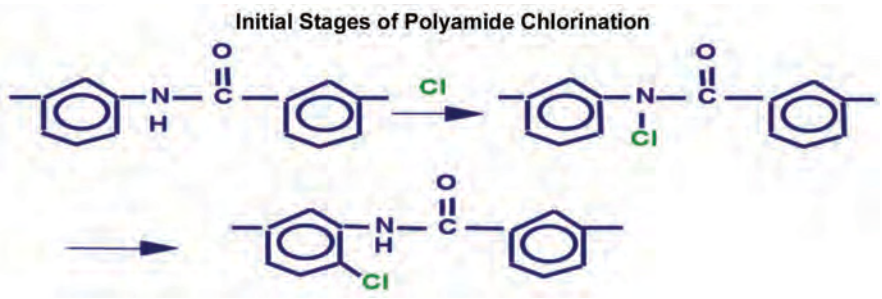

Figure 2. Stages of chlorination of polyamide polymer.

Chlorination – Dechlorination Processes in RO Systems

Due to unpredicted sensitivity of polyamide membranes to the presence of free chlorine and its potential effect on salt rejection properties, the membrane performance warranty terms usually include specification for the allowable level of free chlorine not to exceed a concentration of 0.1 ppm in feed water to the membrane unit.

The general tendency during operation of RO desalination systems is to avoid addition of free chlorine to the feed water on a continuous basis.

In addition to the danger of potential damage to the polyamide membrane, another drawback of feed water chlorination is the generation of conditions which, after dechlorination, could stimulate increased growth of bacterial population in the RO membrane unit.

The prevailing opinion is that free chlorine breaks organic matter present in the feed water to biodegradable fragments. In RO systems, free chlorine is removed from the feed, prior to the RO membrane unit, during the dechlorination step. After the dechlorination step, the bacteria that survived chlorination and have reached the membrane unit, benefit from an increased quantity of nutrients to support their growth.

It has been observed in RO systems treating surface water that the rate of membranes biofouling was higher during operating periods when feed water was chlorinated and dechlorinated than during operation without feed water chlorination.[8]

In some RO applications; however, free chlorine is already present in the water source, added as a disinfectant. Such applications include RO processing of low salinity water that originates from potable water networks and applications in industries that are governed by regulations mandating the presence of chlorine residual in the water source. In the above category are RO units operating to produce process water for food and beverage industries, and for pharmaceutical manufacturing.

In water originated from potable water supply systems, chlorine can be present in the form of free chlorine, chloramines (usually monochloramine), and organic chloramines. Free chlorine and monochloramine residual is introduced to potable water to maintain disinfection residual. Organic chloramines could be formed during chlorination of water sources that contain organic nitrogen compounds (usually at low concentrations). All three types of compounds present in the water source contributed to the measurement of the total (or combined) chlorine.[9]

If any form of combined chlorine is present in feed water sources, it has to be removed prior to feed water entering the RO membrane unit equipped with polyamide membrane elements.

Removal of Free Chlorine Compounds from RO Feed Water

A number of methods have been tested and applied for removal of chlorine (and other oxidants) from RO feed water. All dechlorination processes are based on reduction of free chlorine or chloramines to the chloride ion. For practical reasons, the methods that are currently being applied in commercial systems are limited to two processes:

- Dechlorination by passing feed water through activated carbon filters
- Dechlorination by dosing a solution of sulfite compounds to the feed water stream

In addition to the above, a new process is being implemented in a small number of RO systems. This process, that consists of dechlorination by exposing feed water to UV radiation, provides chlorine reduction without the use of chemicals with the additional benefit of the destruction of dissolved organics and practically complete reduction of bacterial activity in the RO feed water. The UV radiation which is emitted from medium pressure ultraviolet lamps generates a polychromatic light (broader wavelength from 200 nm to 400 nm and above). This is caused due to higher vapor pressure (0.13 – 13 bar) and high temperature (600 – 900°C).

Dechlorination Using Granular Activated Carbon (GAC) Filters

Dechlorination using granular activated carbon filters is a very effective method of free chlorine reduction. The end products of this dechlorination process are chloride ion and CO2 according to reaction:

$$C + 2Cl_2 + 2H_2O = 4\,H^+ + 4\,Cl^- + CO_2 \quad (6)$$

$$C + 2NH_2Cl + 2H_2O = 2NH_4^+ + 2Cl^- + CO_2 \quad (10)$$

The dechlorination equipment in this process consists of activated carbon filters. The flow velocity through the filters is in the range of 5 – 10 m/hr and Empty Bed Contact Time (EBCT) is in the range of 10 – 15 min. The activated carbon bed depth is in the range of 1 – 1.5 m.

Dechlorionation using activated carbon filters has been applied extensively in the past to treat RO feed. It is a very reliable method for reduction of concentration of free chlorine and chloramines. This process also has the capacity to reduce somewhat the concentration of organics present in the feed water.

For RO applications; however, GAC dechlorination also introduces some obstacles into the proper operation of the RO process. The use of GAC for treatment of feed water to the RO system could result in fouling of RO membranes. Membrane fouling that is related to the GAC operation could be caused by one of two processes:

- Release of carbon fines from the carbon bed and subsequent blockage of feed channels of membrane elements, mainly in the lead position in the RO membrane unit.
- Growth of biofilm in the carbon filter and sloughing of biological fragments into RO feed stream causing biofouling and excessive pressure drop in the membrane unit.

The GAC dechlorination process is reliable and the GAC equipment is simple to operate; however, GAC pressure vessels require a significant additional area in the system layout.

Dechlorination Using Sulfite Compounds

Water dechlorination using sulfite compounds relies on reduction-oxidation reaction between sulfur containing compound, at +4 oxidation state, and chlorine. In this process, sulfur is oxidized to +6 oxidation state and chlorine is reduced to chloride ion (-1 oxidation sate). Sulfur containing compounds that are suitable for the dechlorination process may include:

- Sulfur dioxide (SO_2)
- Sodium sulfite (Na_2SO_3)
- Sodium bisulfite ($NaHSO_3$)
- Sodium metabisulfite ($Na_2S_2O_5$)
- Sodium thiosulfite ($Na_2S_2O_3$)

The dechlorination process consists of reaction of S(+4) species, such as sulfite ion (SO_3^{-2}) with free or combined chlorine:

$$SO_3^{-2} + HOCl = SO_4^{-2} + Cl^- + H^+ \quad (7)$$

$$SO_3^{-2} + NH_2Cl + H_2O = SO_4^{-2} + Cl^- + NH_4^+ \quad (5)$$

The above reactions are rapid and result in complete conversion of chlorine compounds to the chloride ion. After addition of sulfite compound to the RO feed stream, a contact time below one minute for free chlorine and below five minutes for chloramines is usually sufficient for complete dechlorination.

Based on the stoichiometry of the dechlorination reactions, the quantity of sulfite compound required per 1 ppm of residual chlorine range from 0.9 ppm of sulfur dioxide (SO_2) to 1.8 ppm of sodium sulfite (Na_2SO_3). In RO applications, the excess of sulfite compound is used, the ratio being around 3:1.

The dechlorination equipment required for sulfite based dechlorination usually is limited to chemical solution storage tanks and dosing unit.

The rate of addition of sulfite compound solution is based on projected residual concentration of free or combined chlorine in the feed water to the RO unit.

The dechlorination process using sulfur (+4) containing compounds is very reliable. However, this process involves supply and management of inventory of dechlorination chemicals and periodic replacement of dosing solution to maintain

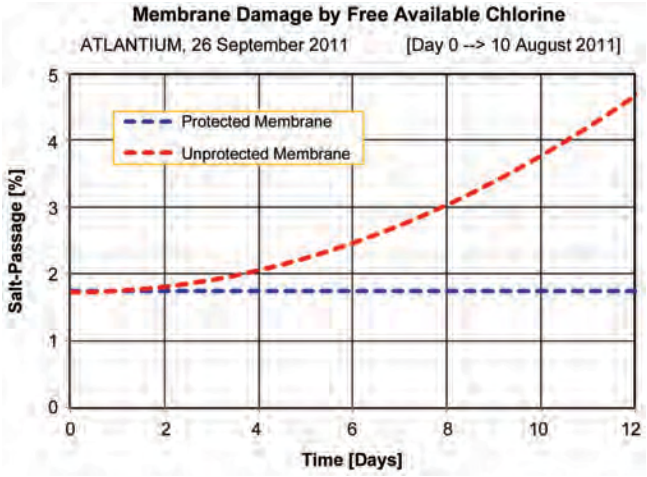

Figure 3. Salt passage (Equation 4) vs. time for two of the membranes studied. The ***protected membrane*** by Free Chlorine Oxidation maintained the salt passage constantly for the study period. The ***unprotected membrane*** for which the Free Chlorine was not Oxidized quickly degraded and the resulting salt passage noticeably increased within a week of operation. The quick rise of salt passage validates the need for adequate and continuous membrane protection ["elimination" of the oxidizing Free-Chlorine molecules (HClO and OCl^-)].

designed concentration of the active ingredient.

RO systems applying the above method of free chlorine reduction, frequently suffer from formation of biofouling layers in the membrane unit.

Dechlorination Using UV Radiation

Use of UV radiation as an alternative dechlorination method that has potential to sufficiently reduce free chlorine without the use of activated carbon or chemicals was postulated and evaluated in the early eighties.[11-14] The initial application considered was removal of free and combined chlorine from water supply to the fish tanks.[11-12]

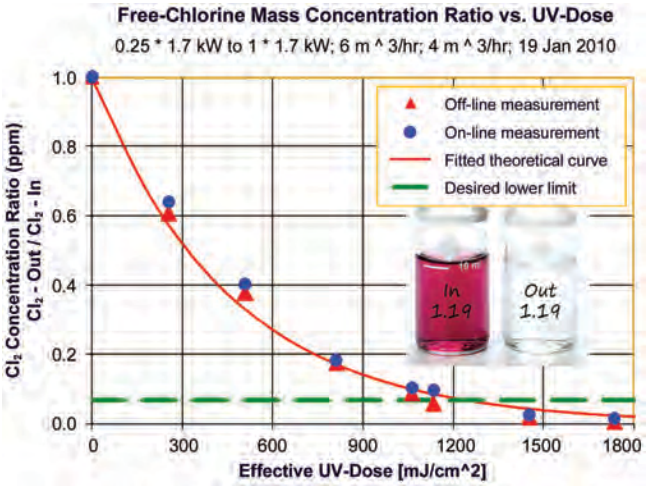

Figure 5. Dechlorination field test. Aqueous chlorine concentration indeed follows an exponentially decaying curve.

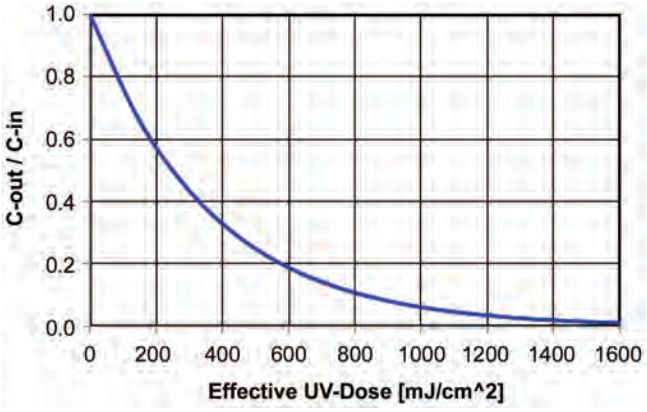

Figure 4. Theoretical decay of aqueous chlorine concentration with increased effective UV Dose. The equation follows $\frac{1}{2}^{(\frac{x}{320})}$ in which x (mJ/cm^2) is Effective UV-Dose and 320 mJ/cm^2 is the UV-Dose required to reduce amount of Free Chlorine by half.

The results of these early works indicated that UV is effective in reduction of free and combined chlorine below the detection limit. Some tests indicated[12] that reduction of free chlorine with UV was more complete than the chlorine reduction using GAC, tested in parallel. However, it was found out that the intensity of UV radiation required for effective dechlorination has to be significantly higher than the UV intensity commonly used for water sterilization.

The dechlorination (or photodecomposition) process consists of absorption of UV photons followed by decomposition of the photon-absorbing molecules:[15]

$$2(HOCl) + 2h\nu \rightarrow 2H^+ + 2Cl^- + O_2 \qquad 16$$

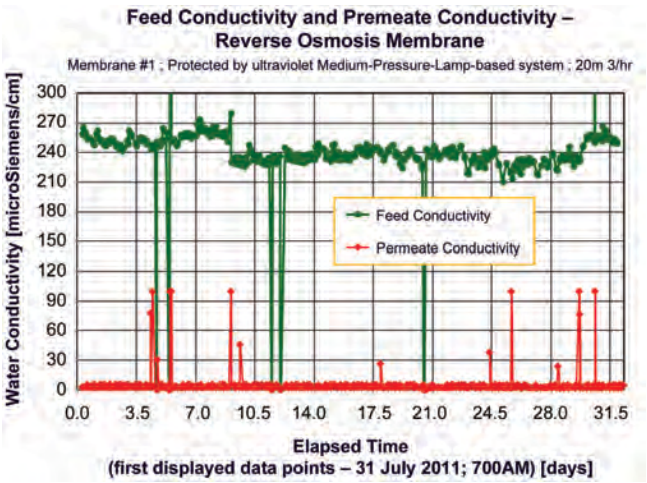

Figure 6. The curves shown relate to the last month of a four-month in-plant operation of a bank of polyamide RO membranes. The RO membrane bank is protected by a dedicated in-line high-power high-intensity MPL-based UV system. Flow-rate through the membrane branch – about 20 m^3/hour (~90 gpm). Average pre-UV chlorine concentration – 1.0 ppm. Past-UV chlorine concentration (in the membrane-feed water) – "below detectable level".

$$2(OCl^-) + 2h\nu \rightarrow 2Cl^- + O_2 \quad [17]$$

Several other photodecomposition processes, some of which involve the intermediate formation of hydroxyl radicals are also discussed in the literature.[18]

The rate of photodecomposition of aqueous chlorine molecules follows first-order kinetics.[18] Meaning – the concentration of aqueous chlorine molecules vs. applied effective UV-Dose follows an exponential decay curve as seen in Figure 3.

Several dechlorination field-tests conducted by Atlantium scientists indeed verify the first-order kinetics theory as seen in Figure 4.

Water conductivity data, collected in a dechlorination field installation from April 2011 through July 2011, verify the effectiveness of the UV membrane protection method. During the four month follow-up period, salt passage through a bank of polyamide RO membranes remained essentially constant as seen in Figure 5.

The installed high-power UV-systems, equipped with high intensity Medium-Pressure-Lamps (MPLs) treated a flow-rate of about 20 m^3/h (~90 gpm) and provided continuous protection to the salt-rejecting RO membranes - *Figure 6*.

Summary

Free chlorine is frequently present in feed water sources utilized by industrial RO desalination systems. RO polyamide membranes are easily damaged by strong oxidants; therefore, any free chlorine compounds have to be removed from the RO feed water.

Reliable dechlorination process alternatives include reduction of chlorine compounds by applying dechlorination with granular activated carbon or by injection of solution of sulfite compound. Both of the above methods have some drawbacks related to handling of additional process chemicals or could contribute to increased rate of fouling of RO membranes.

Both theoretical and experimental data clearly indicate efficacy of UV radiation as an effective chlorine reducing process for dechlorination of RO feed water. The UV dechlorination process is a chemical free method and could provide additional benefit of reduction in membrane fouling rate.

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About the Author

Mark Wilf, PhD, recognized as a global expert for membrane applications, provides expertise to the engineering and scientific community worldwide and participates in professional forums defining future directions for membrane technology and application development. This includes reverse osmosis, nanofiltration, ultrafiltration, and microfiltration technologies applied for water desalination, potable water treatment, and industrial and municipal wastewater reclamation. Dr. Wilf has been involved in process development, system design, project execution, plant operation, and maintenance of large, commercial desalination plants in the US, Europe, and the Middle East since 1977. Dr. Wilf has been involved in development of new desalination processes and optimization of membrane technologies. Some of his inventions have resulted in patent applications and are being used in commercial desalination systems. Dr. Wilf is a member of the Editorial Board of the Desalination Journal, an Advisory Expert to the Middle East Desalination Research Center, and a peer reviewer to number of journals on water treatment. He frequently reviews research projects and publications for these organizations. Dr. Wilf is regular contributor to professional journals. He wrote chapters on membrane technology processes and applications for several books. He co-wrote and edited The Guidebook to Membrane Desalination Technology that was published in 2006. The second book on membrane technology, The Guidebook to Membrane Technology for Wastewater Reclamation, was published in January 2010. Dr. Wilf regularly presents seminars and teaches courses in desalination and membrane technology to engineers and water professionals. His seminars and courses are offered through the European Desalination Society at the University in Genoa, Italy and in San Diego, US. He can be contacted by email at: mark.wilf@ROtechnology.net.

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A Review of Regulations and Developments in GMP and Supply Chain Integrity of Active Pharmaceutical Ingredients

by Sia Chong Hock, Katherine Loh Kai Xin, Vimal Sachdeva, and Chan Lai Wah

This article presents an overview of the current regulations and developments in good manufacturing practices and supply chain integrity of active pharmaceutical ingredients, and analyzes the challenges faced by regulatory authorities and industry.

Active Pharmaceutical Ingredients (APIs) are defined as substances intended to be used in the manufacture of drug products, and when used in the production of a finished drug product, becomes an active ingredient of that product. APIs possess pharmacological properties which are used in the diagnosis, prevention and treatment of diseases in patients, among other purposes.[1] Without APIs, Finished Products (FPs) are nothing more than placebos.

Generally, APIs are manufactured in large production batches. The amount of API in one production batch can be used to make many dosage units of a drug product, sufficient for ~10,000 to 200,000 patients or more. Hence, quality defects in one batch can affect many patients.[2] In 2008, serious allergic reactions resulting in more than a hundred deaths occurred in the United States (US) after patients were injected with heparin - *Figure 1*. Investigations by the US Food and Drug Administration (FDA) led to the identification of the contaminant, oversulphated chondroitin sulphate (OSCS), in significant quantities (~5 to 20%), in the affected batches. At least 10 other countries also reported the presence of OSCS in heparin APIs.[3]

The quality of APIs is a major determinant of the quality of FPs.[4] An API of the required quality can only be produced with rigorous control of its manufacturing process.[5] For instance, if production of Rifampicin API is not well-controlled, the formation of larger particles that are less soluble, could lead to poorly effective drugs that may cause drug resistance in the treatment of tuberculosis.[4,6,7] The dissolution profiles of various size fractions of a commercial rifampicin sample, RIF-4, show that particles above 100 microns have poorer dissolution - *Figure 2*.[6]

Thoroughly validated manufacturing processes also are needed to ensure the formation of only the desired isomeric and polymorphic forms.[8] The thalidomide tragedy of the 1960s that led

Figure 1. Heparin Injection linked to serious allergic reactions.

to many severe birth defects as seen in Figure 3 was attributed to teratogenicity caused by one of the two enantiomers of thalidomide.[9-11]

Overview of Current API Manufacturing

The API component alone can account for more than 80% of the price of the FP.[4] The pharmaceutical industry in the US and European Union (EU) is increasingly turning to overseas manufacturers of APIs[12] due to economic reasons as well as the relatively less stringent regulations abroad.[13]

Currently, China produces ~70% of the world's generic APIs, while India produces about 19%.[14] About 80% of APIs used in the US and EU for the manufacture of drug products come from foreign countries, mainly China and India.[15] A large number of manufacturing facilities in China and India are operating under standards that are nowhere near those of the Western world.[16] Illegal activities are also known to exist among manufacturers of APIs in these regions.[17]

Overview of Regulations on GMP and Supply Chain Integrity of APIs

Ensuring GMP compliance and supply chain integrity of APIs is key to assuring their safety and quality.[19,20] Details of regulations by various RAs on GMP and supply chain integrity are listed in Table A. In general, manufacturers of APIs are regulated less stringently as compared to FP manufacturers.[21] Inspection coverage of foreign manufacturing facilities is inadequate.[21-26] Many APIs used in EU and US are made in Asian facilities that have never been inspected.[15,27] Current EU legislation does not require mandatory inspections of suppliers of APIs.[28-30] In general, regulators have not kept pace with the globalization of API market.[5]

National and International GMP Requirements for APIs

The World Health Organization (WHO) GMP for APIs are described in Chapter 2 of the WHO compendium: "Quality Assurance of Pharmaceuticals."[57] The US, EU, Japan, and PIC/S Participating Authorities (PA) have adopted the International Conference on Harmonization (ICH) Q7A which is a consensus document between the authorities and the industry.[41]

However, there are countries that rely on their own national GMP guidelines. For example, in India, Schedule M of the "Drugs and Cosmetics Rules" is adopted.[59] In China, the GMP code is the Chinese State Food and Drug Administration (SFDA, now known as CFDA or China FDA) GMP for Pharmaceutical Products. In both cases, the GMP rules governing APIs do not have the same rigor as that of ICH Q7A, which has been developed exclusively for APIs.[58] The objective in API processing is to achieve a pure compound of certain identity and quality, whereas that of FP manufacturing is to achieve uniform distribution of the API within the dosage form.[46] Hence, a GMP guide developed for FP manufacturers may not be so suitable for API manufacturers.

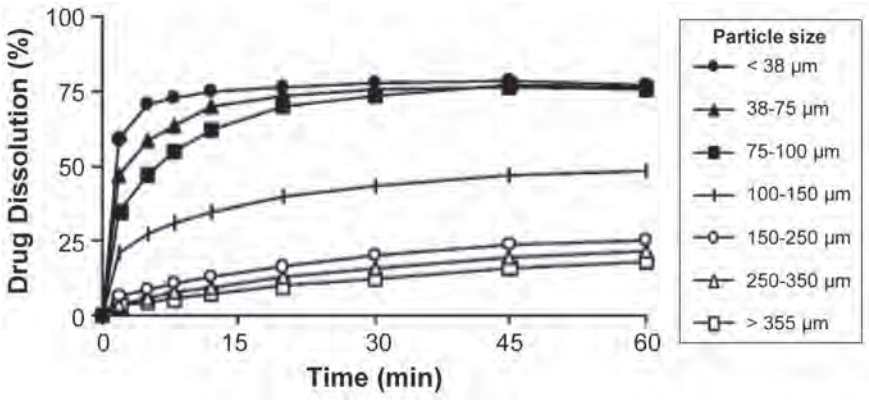

Figure 2. Dissolution profiles of size fractions of a commercial rifampicin sample, RIF-4.[6]

Differences in GMP Standards and their Impact on API Quality

There are provisions found in ICH Q7A that are not covered by Schedule M or SFDA GMP. For example, "Change Control," in ICH Q7A mandates that FP manufacturers be notified of changes that can affect the quality of the APIs."[1] However, Schedule M does not specify procedures for change control.[59] Although "Change Control" is covered in SFDA GMP (2010 Revision),[60] there is no stipulation of the need to notify FP manufacturers of changes that can affect the quality of the APIs. Hence, FP manufacturers who import APIs from China or India could remain unaware of process changes at the manufacturing sites that may impact the quality and safety of their APIs.

Differences in physicochemical properties, stability, and impurity profile also have been reported for APIs manufactured in accordance with the national GMP guidelines of India and China, when compared to APIs manufactured in accordance with ICH Q7A.[63]

Good Distribution Practice (GDP) and Supply Chain Integrity

Distribution is an important activity in the pharmaceutical supply chain – the "family tree" tracing the history of the API from its manufacture and supply to FP manufacturers, to the distribution of the dosage forms to wholesale dealers and pharmacies. The supply chain can be very long with potential and real risks of degradation, contamination, counterfeiting, and falsification.[72] It is therefore crucial to protect the pharmaceutical supply chain against such undesirable activities.

Worldwide efforts to protect the integrity of pharmaceutical supply chains are ongoing and evolving.[66] However, the number of supply chain players such as brokers, traders, distributors, re-packagers, who have (wittingly or unwittingly) allowed the API supply continuum to be interfered, is ever-growing.[64,65]

Degree of Implementation of GDP on APIs

Currently, there is no information in the US Pharmacopoeia and National Formulary (USP–NF) on GDP.[66] Approaches to ensure supply chain integrity vary with individual companies, and current guidelines do not address supply chain integrity

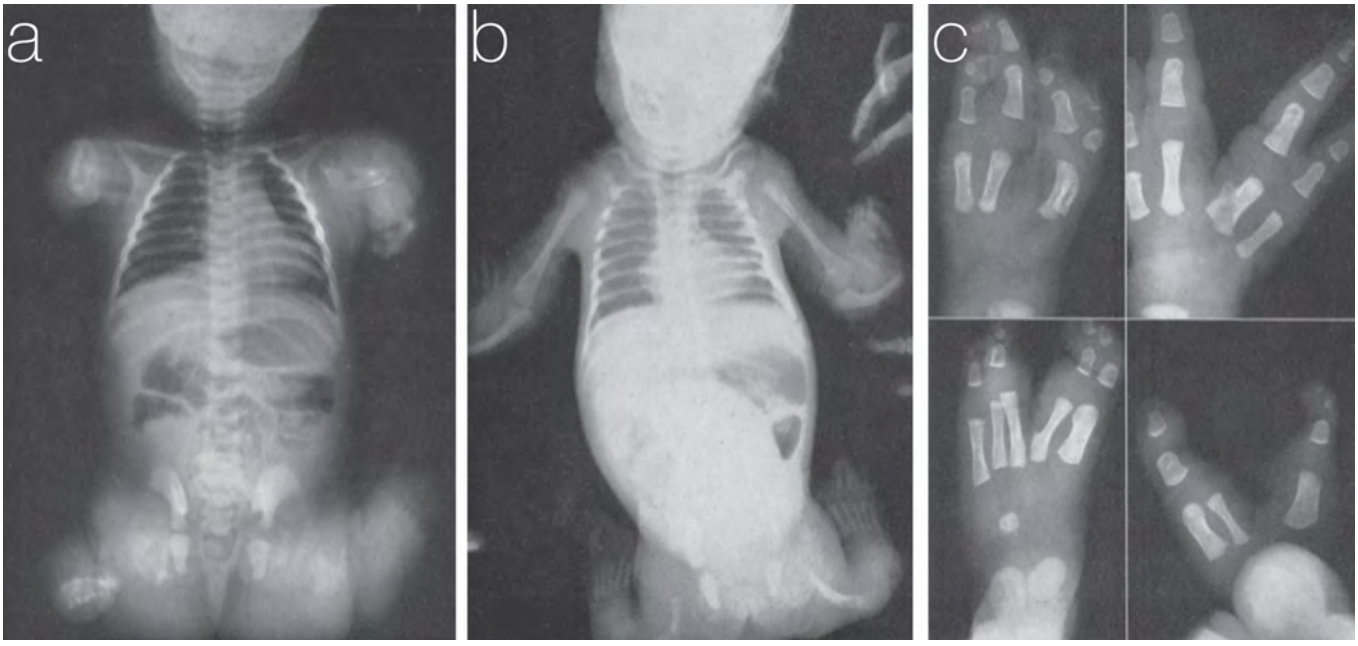

Figure 3. Radiographs of thalidomide-induced birth defects: (a) Phocomelia of all limbs (b) Bowing and angulation of long bones (c) Cleft hands and feet with fusion of some digits.[11]

holistically.[67] The General Chapter <1083> GDP: Supply Chain Integrity in the USP-NF is still a draft. Furthermore, the recommendations in this chapter are non-mandatory.[67]

The PIC/S GMP for APIs, which is equivalent to ICH Q7A, requires manufacturers to ensure that the transportation contractor for APIs follows the appropriate transport and storage conditions.[68] However, there is no guidance on how this should be done and documented as proof. The requirement for proof is only briefly mentioned in a PIC/S "Q&A" document.[69] Also, the way to deter falsification of labels has not been addressed.[68] Although FP manufacturers are required to assure integrity of API supply chain with the help of documentation,[68] the methods for documenting are not stated. Furthermore, based on the PIC/S GMP for APIs, FP manufacturers are required to review supply chain periodically,[68] but there is no clear definition for "periodically." Regulatory requirements for inspecting API supply chains are also apparently absent.[69] Fortunately, recommendations from the Expert Circle on GDP has been adopted recently by PIC/S, and this may lead to better distribution and supply chain controls.[70]

The WHO GDP for Pharmaceutical Products does not cover APIs.[71] In addition, the WHO Good Trade and Distribution Practices for Pharmaceutical Starting Materials,[72] which include APIs, relies on FP manufacturers to test each batch of APIs for compliance with specifications. Inspection and regulatory control of the API supply chain are not covered.

Currently, the European Medicines Agency (EMA) relies on the declaration signed by the QP to verify API supply chains. Amendments to GMP requirements to introduce a pedigree concept for APIs have been proposed, but is still a draft.[34,73] FMD (2011/62/EC), which addresses oversight of players in the supply chain,[65] is now in place. However, scarcity of funds and resources may hold up the implementation of FMD.[29] As of 2 January 2013, FP manufacturers are required to audit their API suppliers for compliance with GDP.[40,74]

The European Fine Chemicals Group (EFCG), which represents EU manufacturers of fine chemicals (including APIs), continues to urge regulators to increase enforcement against rogue players in the API supply chain.[75,76] Inadequate control of the storage and distribution of supplies may represent just

Regulatory Authorities	Regulations on GMP and Supply Chain Integrity of APIs
European Medicines Agency	• FP manufacturers are required to audit API manufacturing sites[16,26,29,31] and declare GMP compliance in marketing authorizations.[16,32] • Non-routine regulatory inspections are based on risk,[33] suspicions of non-compliance or via request from FP manufacturers.[26] • Activities of distributors, traders, agents and brokers are outside scope of legislations.[34] • No registration scheme in place for manufacturers, importers or distributors of APIs.[35] • A Falsified Medicines Directive (FMD) is in place. With effect from 2 July 2013, APIs imported into EU have to be accompanied by a written confirmation from the competent authority of the exporting third country (TC), specifying that the standard of GMP and overall regulatory control of the plant are equivalent to those in the EU.[36-40] • Proposal for mandatory notification of manufacturers and importers of APIs, with particulars to be made available in a Community database. • Proposal for mandatory regular GMP audits of suppliers of APIs by Qualified Person; third-party audits by accredited companies may also be considered.[109,134] • Enhanced GMP inspections of API manufacturers, whereby RAs shall inspect if there is suspicion of non-compliance with GMP, and repeated inspection if GMP in TC is not equivalent to that of EU.[34] • API suppliers are audited at intervals not exceeding 3 years, by or on behalf of the Market Authorization Holder (MAH); only APIs made according to GMP should be used.[31,41-44] • MAH inspected by MHRA for compliance on a 2-year cycle and are expected to periodically re-evaluate suppliers' status.[43] • MHRA will be introducing effective, proportionate and dissuasive penalties for non-compliance.[35]
United States Food and Drug Administration	• Non-compliance with GMP for APIs constitutes a violation of the Federal Food, Drug and Cosmetics Act, which requires all drugs to be manufactured in conformance with cGMP. • ICH Q7A used for inspecting manufacturers of APIs.[46] • Pre-approval and routine inspections on all API manufacturing sites conducted for prescription-only-medicine (POM) sold in US.[47] • FP manufacturers verify API batches with an identity test (with additional testing periodically to validate supplier's results); no explicit requirement to conduct on-site audits.[27] • Foreign firms dealing in APIs which are imported into US are subject to registration and listing.[49]
Health Canada	• FP manufacturers test APIs upon receipt if supplier is uncertified (e.g. audit report unavailable or is more than 4 years old).[50] • Recent amendments to the Food and Drug Regulations will extend GMP requirements to all APIs.[51] • New record-keeping requirements to trace APIs from beginning to end of manufacturing process.[51]
Australia Therapeutic Goods Administration	• Sponsors are responsible for obtaining GMP clearance for overseas API manufacturers via Mutual Recognition Agreements (MRAs) or TGA on-site audits.[52,53] • APIs are registered or listed in the Australian Register of Therapeutic Goods (ARTG).[53] • Registration of OTC products include justification for accepting test specifications of FP manufacturers.[54]
Singapore Health Sciences Authority	• Mandatory licensing is not yet extended to APIs under Health Products Act (HPA).[55] • A voluntary scheme is available for manufacturers of APIs who wish to apply for a GMP certificate.[56] • Form A Licence is required for the importation, storage and supply of pharmaceutical raw materials that are legally classified as Poisons.

Table A. Regulations on GMP and supply chain integrity of APIs.

as much of a risk as failing to control their production.[77]

International Efforts and Challenges Ahead

Increasing globalization and multiplication of players in the API industry have made it necessary to harmonize regulatory requirements, inspections for GMP compliance, and exchange of information.[78,79]

Harmonization of GMP Standards for APIs

The publication of ICH Q7A was a significant step toward a harmonized GMP standard for APIs.[41] The WHO has since revised its GMP Guidelines for APIs to follow the principles of ICH Q7A.[61] Since then, SFDA also has updated its GMP standard to include more of the provisions from ICH and WHO standards. Chinese manufacturers are now in a transition phase.[15]

A new consultation procedure entitled "Harmonization of PIC/S and EMA GMDP IWG Consultation Procedures" has been developed to improve harmonization between EU and PIC/S GMP Guides and related documents. This will keep both parties informed of any revisions of current documents and facilitate their document adoption process.[70]

Several GMP workshops around the world have been sponsored by the US FDA to educate regulators and manufacturers on cGMP compliance.[64] For example, in 2005 and 2006, GMP training workshops were conducted in China and co-sponsored by the US FDA, International Society for Pharmaceutical Engineering (ISPE), and Peking University.[80]

Challenges Faced by Regulatory Authorities (RAs)

Regulatory Landscapes in China and India

Lack of Resources, Expertise, Understanding, and Commitment to GMP

GMP compliance has been less than satisfactory, as demonstrated by the number of warning letters,[15,18,63] import stoppages, and other prohibition orders issued by the US FDA and other RAs.[81] Adhering to manufacturing standards has been difficult and costly, resulting in the closure of many Chinese and Indian companies when GMP was made mandatory.[27] Many Chinese manufacturers are not ready to meet SFDA GMP (2010 Revision).[15] It is estimated that tens of billions of US dollars are needed to upgrade manufacturing facilities and infrastructure.[82] Because of the large number of companies and manufacturing personnel, it will take some time and considerable education to implement the SFDA GMP (2010 Revision).[83]

Poor GMP Enforcement

In some countries, GMP standards may have been adopted, but not actually enforced.[84] Sometimes, non-compliant manufacturers are not forced to close because of government policy supporting the local industry. In other cases, it is the lack of regulatory capacities that results in poor GMP enforcement.[85]

Furthermore, whether a specific API is considered a drug substance, and therefore subjected to regulatory oversight, is often left to the regulator's discretion.[86] It has been reported that with corruption and loopholes in the drug supervision system within SFDA, such loose rules could be changed by officials to serve their own interests,[87,88] and this can lead to poor GMP enforcement. Chemical manufacturers in China are exempted from inspection by domestic officials even if they produce APIs,[3,89] as in the case of Scientific Protein Laboratories-Changzhou (SPL-CZ), the factory that was implicated in the 2008 heparin scandal.[89]

Lax Regulations on APIs Manufactured for Export and Deceptive Practices

Controls on quality of products made for export are much less rigorous than those manufactured for the domestic market.[4,16,27,91] In fact, pharmaceutical products made in China for export does not fall under the jurisdiction of SFDA.[82,86] Certified API manufacturers have been reported to use other lower cost, uncertified sites, to supply APIs intended for export.[18,27,39] Inspectors and FP manufacturers who import these APIs may remain largely ignorant of these deceptive practices.[90] It also has been reported that approximately 3,000 API manufacturing sites in China have been producing large volumes of APIs under conditions which are not GMP-compliant, and these APIs have entered the legitimate global supply chains.[2]

Manufacturers and distributors are also known to falsify documents, records, and labels.[2,23,92] In 2008, it was reported that Ranbaxy, an Indian manufacturer had allegedly submitted false test data to the US FDA. European inspectors also have uncovered constructed façades, where APIs sourced from elsewhere were falsely relabeled at these facades, as though they were produced in the GMP-inspected and approved facilities.[2,27]

Inadequate Foreign Inspections

In general, RAs lack the resources and authority to inspect foreign facilities with meaningful regularity. With increasing number of foreign API sites, the challenge for RAs to conduct regular inspections, will continue to persist, and be further aggravated.[63]

On average, the US FDA only managed to inspect foreign facilities once every nine years. In 2010, the US Government Accountability Office (GAO) reported that as many as 2,394 overseas plants on the FDA's inspection planning list have never been inspected,[27] including SPL-CZ.[94] The US FDA relies on its staff to volunteer for foreign inspections.[15] In addition, inspections are pre-announced such that foreign firms can have more than one year to prepare.[15,95] They could be GMP-compliant when inspected, but lapse in practice once the inspectors leave the facilities, since chances of re-inspections are low.[95] There is little flexibility for extending

on-site inspections even if problems occur. Language barrier is another obstacle.[15] There also were cases when FDA investigators were denied access.[27,92] Despite the US FDA having established offices in China and India to coordinate inspections, the focus is not on APIs. The key concerns of the US FDA in China and India are food and generic drug products respectively. EU agencies appear to be conducting inspections based on geographical proximity to the manufacturing sites instead of risk assessment.[97] The FMD is reliant on QPs to verify compliance of overseas API manufacturers to EU standards, instead of relying on counterpart RAs to perform mandatory inspections.[17]

Inherent Problems with ICH Q7A

The involvement of the (innovator) pharmaceutical industry in the ICH has led to criticism that quality guidelines developed by ICH reflect the standards of high-income countries, and they are too costly for manufacturers in developing countries to meet.[85] In addition, uncertainties with interpretation of ICH Q7A exist, and implementation of ICH Q8, Q9, Q10, Q11 principles into GMP for APIs, has led to non-harmonized interpretations and new expectations beyond the intent of ICH Q7A.[98] For example, SPL-CZ defended that its testing regime was consistent with ICH Q7A, which states "Impurity profiles are not normally necessary for APIs from herbal or animal tissue origin." Thus, CPL-SZ did not deem it necessary to establish impurity profile for the heparin API.[77]

Recommendations for Improvements

Improving Oversight of Foreign Manufacturers

GMP compliance by manufacturers of APIs can only be enforced if regulatory inspections and API supplier audits are mandatory, and re-inspections take place regularly.[14] RAs could consider GMP inspection collaborations via Mutual Recognition Agreements (MRAs), memoranda of understanding,[99] or through utilizing existing GMP certification approaches.[79] Collaborations can bring about greater information sharing and coordinated deployment of resources, which can in turn facilitate regular inspections and re-inspections[41,100] of foreign API manufacturing sites by focusing on comparability.[101]

Intelligence gathering[13,99,101] for increased vigilance on counterfeits and adulteration should be expanded. Signals detected, e.g., significant changes in availability or price of an API, should be promptly shared to enable other RAs to allocate resources to high-risk API manufacturing sites.[13,102]

Getting industry to pay an inspection fee can be a useful strategy to increase regulatory resources for inspections. Both the Bulk Pharmaceutical Task Force (BPTF) and EFCG have agreed to the US FDA Generic Drug User Fee Act (GDUFA).[12,92] Under GDUFA, the global generic industry will provide the US FDA with close to $300 million per year in fees for improved oversight of overseas API manufacturers.[103] RAs also should have accurate data of overseas API manufacturing sites exporting to their countries, to develop an evidence-based estimate of resources[96,103] needed to carry out their inspections. Inspectorate groups focused[48] on inspecting overseas API manufacturing sites also could be considered to increase commitment to overseas inspections. Unannounced inspections could be explored to improve GMP compliance. However, close cooperation and coordination with inspectors in TCs are needed to achieve this goal.[27]

FP manufacturers could be mandated to carefully assess suppliers prior to their engagement, with on-site audits performed periodically.[27,104,105] Audit procedures should be standardized, and guidance documents developed to prevent FP manufacturers from being pressurized to accept a supplier based solely on cost considerations.[15,106]

More independent entities could be accredited by RAs to perform foreign inspections on their behalf.[15,107] Also, FP manufacturers should be encouraged to participate in the USP Drug Substance Suppliers Qualification Program[108] and similar schemes, to ensure better quality assurance of API suppliers. Accredited third-party audits may overcome the lack of audit independence by QPs, who may be bound by economic considerations of its MAH.[109] Sanctions and deterrence[16,48,97,105] also should be in place to deter FP manufacturers from accepting a supplier based solely on cost considerations and to prohibit operations of non-compliant API manufacturers.

Controls on export-only medicines should be tightened. Despite repeated calls for equivalent regulations to be applied to both pharmaceuticals intended for domestic use and for export, lax regulations for export-only medicines still exist in many countries.[4] Chemical manufacturers producing APIs should be subject to mandatory GMP inspection and regulated like pharmaceutical manufacturers.[86,89]

Improving Manufacturing Standards and Regulations

Western regulators (especially those in Asian offices) could do more to acquaint Asian officials and manufacturers with western drug quality standards and enforcement policies.[107] Strengthening oversight by RAs in countries where APIs are manufactured would be critical for added control.[23,83] Inspectors from developing countries should actively participate (as observers) in inspections organized by WHO Prequalification Program (PQP) as part of their capacity building.[110] FP manufacturers should regularly assess and provide feedback on suppliers' performance, and coach them if necessary to improve GMP compliance.[14,43] Instead of outsourcing API manufacturing, pharmaceutical companies may consider setting up their own operations[111,112] in foreign territories.

Implementing Supply Chain Pedigree

Technological advances, such as Radiofrequency Identification (RFID), two-dimensional bar code,[113,114] and other technologies to authenticate sources of APIs, may help counter

deceptive practices. The pharmaceutical sector could learn from other industries that have successfully implemented such sophisticated technologies. Many barriers continue to stall implementation of electronic pedigree that was supposed to take effect in 2000 as mandated by the US Prescription Drug Marketing Act.[113,115] The parties involved should speed up their work so that any potential benefits of electronic pedigree could be extended to the API market.

Continual Review of Test Methods to Detect Impurities

Standard analytical tests for detecting process-related impurities are no longer adequate in detecting economically motivated adulteration,[2] as in the case of OSCS presence in heparin.[58,64,94,104,116] FP manufacturers should use analytical technologies that are most capable of identifying and quantifying impurities in APIs.[113] Analytical tests need to be continually updated so that they can detect suspected adulterants and contaminants.[3,27,116] Updates on specific test methods should be shared with other countries[117] to help detect contaminants in their corresponding products.[64,94] Enhancing and sharing technologies for signal detection[3,102] can aid in identifying APIs at highest risk of economically motivated adulteration, and hence, allow sufficient time for the regulator and industry to design additional tests. The various pharmacopoeias (USP, EP, JP, BP) should collaborate[118] to identify APIs at risk of contamination and to recommend methods to prevent and rapidly detect contaminations.

International Collaborative Initiatives

Pharmaceutical Inspection Convention/Cooperation Scheme (PIC/S)

PIC/S is the leader in the collaboration and harmonization of drug inspection practices and GMP standards.[92,119] PIC/S encourages risk-based inspections[92] and has produced a simple and science-based Quality Risk Management (QRM) tool that may be used by inspectorates when planning frequencies and scope of GMP inspection.[120,121] FP manufacturers may customize this tool for auditing API suppliers. Since the majority of inspectors are more familiar with inspection of FPs, PIC/S has produced an aide-memoire for API inspection to harmonize the approaches for inspections of API manufacturers.[122] An international API inspectors training program also has been established to harmonize interpretation and application of ICH Q7A to API suppliers inspections.[70,123] A procedure for notifying all PIC/S members of quality defects and falsification in APIs is also in place.[124]

Unfortunately, not all key API players, e.g., China, India, and Japan, are PIC/S members yet.[78] Japan has applied in 2002, while China has recently expressed interest to join PIC/S.[92] In some countries, there are legal impediments that prohibit sharing of GMP inspection reports between RAs.[79] Also, specifically in the case of the US FDA, current legislations do not permit the utilization of inspection reports of other RAs for drug approvals. Changes to US legislations, and the mindset that US FDA GMP inspections represent "the so-called Gold Standard," are needed for full benefits of

Come 2014, PIC/S will be restructuring itself to include new sub-committees, such as those for training, compliance, GMP/GDP harmonization, risk, audit, and budget. As each sub-committee focuses on specific core areas, it is likely that the effectiveness of PIC/S would be further enhanced.[70]

International API Pilot Program

An international API pilot program was conducted from December 2008 to December 2012. This API pilot program involved international collaborations by TGA, EMA, and the US FDA with the aim of rationalizing international GMP inspections.[125] This pilot program was successful in getting the collaborators to agree to the maintenance of cooperation and to further extend participation.[12] It promoted exchange of information on inspections and reports[42] and joint API inspections for confidence building, and for identifying differences in inspection practices or GMP interpretations.[126] Information from past inspections of more than 640 sites of mutual interest was entered into a central database and a master list of API supplier facilities was established.[92,119] This has resulted in less duplication of routine inspections,[92,126] which in turn, reduced the workload of regulators and inspection fatigue for API manufacturers. It also has enabled greater inspection coverage of API manufacturing sites using lesser resources. The EMA and the US FDA will be waiving some routine post-authorization or surveillance inspections in each others' territories to free up resources for inspections in other high-risk countries.[128]

Participants of the API pilot program are now working toward identifying and establishing a secure host for sharing data in real-time.[127] This will enhance the efficiency of the existing approach which relies on forwarding of GMP reports, resulting in delays in transmission of information. Participants also supported the idea of preparing one single inspection report that could be used by all stakeholders to maximize the benefits of the project.[127]

Currently, US legislations mandate the redaction of inspection reports.[127] The US FDA has conceded that increased information sharing with counterparts would be easier if it did not need to redact commercially sensitive information from inspection reports. It also has suggested the formation of a "global coalitions of regulators" that allows countries to maintain sovereignty in setting standards and making decisions, but relying more on the work of other regulators and pooling of resources to manage the global pharmaceutical inventory.[129]

WHO Prequalification Program (PQP) for APIs

The WHO Prequalification Program (PQP) facilitates access to good quality medicines through assessment of the prod-

ucts and the inspection of their manufacturing sites. Since good-quality APIs are vital to the production of good-quality medicinal products, the WHO PQP also has started a pilot project recently to prequalify APIs.[61,130] An API submitted for evaluation will undergo dossier assessment and inspection of the manufacturing site before inclusion in the WHO List of Prequalified APIs.[130] Inspections may be waived if inspection findings by another acceptable organization like PIC/S and/or ICH are positive. GMP compliance will be confirmed at least once every four years, with the usual interval being two to three years.[61]

WHO Public Inspection Reports (WHOPIR) are published on its website. The decision to prequalify an API is subject to change whenever new information is available or known to WHO. If serious safety and/or quality concerns arise in relation to a prequalified API, WHO may suspend the API until the investigative results have been evaluated, and the issues resolved. Hence, users of WHOPIR should have their own internal measures or mechanisms to ensure that manufacturing practices have not lapsed since the previous WHO inspection.[131] It should be mentioned that the above program currently covers only medicines and associated APIs used for HIV/AIDS, malaria, tuberculosis, and for reproductive health.

Rx-360 and Shared Third-Party Audits

The pharmaceutical industry has come together to establish an international pharmaceutical supply chain consortium, which brings together the complete global supply chain players, including innovators and generics, primary and secondary manufacturers, and middlemen;[97] hence, its name, "Rx-360." Participants can leverage the results of one another's API supplier audits[27] to reduce duplication and "audit fatigue." Rx-360 also works with research organization to develop new technologies to prevent or detect adulteration and conduct supply chain surveillance.[132] The Rx-360 Supply Chain Security Guide for Audits[133] addresses the security of facilities, materials, and documentation. It also checks for distributors' compliance with GDP. Members are required to report suspicious events to the consortium, which then disseminate the information and possibly develop potential proactive solutions for its members to consider adopting.[132] An audit shared by several FP manufacturers can save resources.[109,134] Diapharm (Münster, Germany)[135] and the APIC Audit Programme[134] provide such a shared service. This is acceptable to the RAs of EU if the QP ensures the scope of audit is applicable.[109,134] Qualifications of third-party auditor should be verified;[136] however, it is thought that third-party audits may dilute the responsibility of pharmaceutical companies.[137]

Conclusion

The current challenges in GMP compliance and supply chain integrity of APIs, including the issues of contaminated, adulterated, counterfeits, and falsified APIs that are picked up from time to time by regulators, may be the "tip of the iceberg." As more countries tighten regulations on GMP and supply chain integrity, and step up their enforcement activities, the safety and quality of APIs can be expected to be further assured. Although, some of the leading RAs have begun tightening regulations for APIs, the progress is relatively slow.

The ICH, WHO, PIC/S Expert Circles on APIs and GDP, and the international API pilot program (co-driven by the US FDA, EMA, and TGA), have all contributed substantially to the harmonization of API regulations. PIC/S membership has grown to 43 PAs[70] (as at January 2013), and all members have adopted ICH Q7A. Collectively, these international and national agencies can do much more to accelerate greater collaboration and harmonization of regulations on GMP and supply chain integrity, leading ultimately to a win-win-win outcome for the regulator, the pharmaceutical industry and consumers, globally.

List of Abbreviations

API	Active Pharmaceutical Ingredient
ARTG	Australian Register of Therapeutic Goods
BP	British Pharmacopeia
BPTF	Bulk Pharmaceutical Task Force
CoA	Certificates of Analysis
EFCG	European Fine Chemicals Group
EMA	European Medicines Agency
EP	European Pharmacopeia
EU	European Union
FDA	Food and Drug Administration
FMD	Falsified Medicines Directive
FP	Finished Product
GAO	Government Accountability Office
GDP	Good Distribution Practice
GDUFA	Generic Drug User Fee Act
GMP	Good Manufacturing Practice
HC	Health Canada
HPA	Health Products Act
HSA	Health Sciences Authority
ICH	International Conference on Harmonization
JP	Japan Pharmacopeia
MAH	Market Authorization Holder
MHRA	Medicines and Healthcare products Regulatory Agency
MRA	Mutual Recognition Agreement
OSCS	Oversulphated Chondroitin Sulphate
OTC	Over-The-Counter
PA	Participating Authority
PIC/S	Pharmaceutical Inspection Convention/ Cooperation Scheme
POM	Prescription-Only-Medicine
QP	Qualified Person
RAs	Regulatory Authorities
RFID	Radiofrequency Identification

SFDA	State Food and Drug Administration (now known as CFDA or China FDA)
TC	Third Country
TGA	Therapeutic Goods Administration
US	United States
USP-NF	US Pharmacopeia and The National Formulary
WHO	World Health Organization
WHO PQP	WHO Prequalification of Medicines Program
WHOPIR	WHO Public Inspection Reports

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Editor's Note: please visit www.pharmaceuticalengineering.org to view the References, in their entirety.

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Are You Controlling Your Boundary?

by Stephanie Wilkins, PE

This article clarifies what constitutes a segregated and dedicated facility and discusses the risk of cross contamination if the boundary is not managed properly.

In April, the FDA published the Guidance for Industry **Non-Penicillin Beta-Lactam Drugs:** *A CGMP Framework for Preventing Cross-Contamination*. The document expanded upon the long-standing requirements associated with penicillin manufacturing by including similar expectations that all non-penicillin beta lactams (in addition to penicillin products) be manufactured in segregated and dedicated facilities. The guidance also states that each of the five classes of beta-lactams (penicillins, cephalosporins, penems, carbacephems, and monobactams) should be manufactured in separate segregated and dedicated facilities from each other.

The expectations may seem fairly straightforward indicating that risk-based approaches are not useful with these compounds. Nothing could be further from the truth.

First let's start with the actual regulatory requirements. Verbiage contained in both the FDA's Code of Federal Regulations and EMA's Manufacturing Annex requires that segregated and dedicated facilities be utilized for the manufacture of penicillin. From a compliance perspective, the FDA and EMA have maintained that this requirement does not necessarily mean a separate building. Over the last several decades, ambiguity and misinterpretation of the requirements have resulted in many manufacturers taking the highly conservative route of dedicating buildings – and even a more conservative approach by dedicating sites to the manufacture of beta lactams. In some instances, these may have been justified, but in many cases, that is not true. In fact, many installations of these dedicated buildings on multi-product sites are actually not managing the risk of cross contamination – but are adding to the inherent risks that exist.

While the regulators have communicated that they are not in support of a threshold value/Acceptable Daily Exposure (ADE) for these compounds, other aspects of ISPE's Risk-MaPP Baseline® Guide are relevant for managing the risk of cross-contamination from beta lactam products.

Fundamentally, the concept is to create a boundary which controls the entry and exit of product. The area outside the product boundary is considered "safe" and should not contain open product that could potentially cross-contaminate another product. Note this is the same concept for all products, not just beta lactams. When dealing with beta lactams, this compound boundary is the boundary of the segregated and dedicated space that can be a suite or suites within a building, a separate building or separate site.

In Figure 1, a typical site arrangement is shown where there is an administration building (Building A), warehouse and three manufacturing buildings. Let's assume one of the manufacturing buildings is dedicated to penicillin products (Building B), one is dedicated to cephalosporin products (Building C), and the other manufactures general products not in the beta lactam family (Building D). Note for Buildings B and C, the product boundary is the building boundary as only the same family of beta lactams is permitted in either facility. Building D is a multi-product facility which requires a more detailed assessment not only at the building boundary, but also within the facility at each of the product/compound boundaries.

The risk assessment effort in this scenario is to analyze the risk that product or product residues from Buildings B and C do not penetrate the building envelopes (the product boundary) for possible cross-contamination with each other or with Building D.

Figure 2 shows a dedicated and segregated suite within a multi-purpose facility. For the space to be segregated, the walls between the suite and the other rooms must extend from structure to structure with all penetrations sealed to be leak tight, have independent HVAC, and backflow prevention on any utilities that serve the dedicated and segregated suite from the multi-purpose facility. If the controls are established from a meaningful risk assessment process and accompanied by the appropriate procedures for employee and material movement, there should be no reason why beta lactams cannot be processed in the facility.

As such, the key is to assess the controls at the product boundary. ISPE's Risk-MaPP Baseline Guide is an important tool as it provides an approach to completing and documenting these assessments.

ISPE's Risk-MaPP Baseline® Guide states there are four modes by which cross contamination can occur; mix-up, retention, mechanical transfer, and airborne transfer. To ensure that the risk of cross contamination is controlled, an assessment of the four potential modes should be completed.

Starting with the potential for mix-up, reviewing all procedures in place to ensure the right materials, people and equipment are in the areas they should be. It is especially important for sites that manufacture beta lactams to establish and monitor procedures on how materials, people and equipment transit the site. It is essential that the procedures and methods be clearly defined so that any deviations from the requirements are identified and addressed. Some items to consider may be the use of color-coded gowning/uniforms and labels so that it is easier to identify if something is in the wrong place. Use of electronic access control can help further ensure that people – and even equipment and materials are only allowed to enter the facilities that they are allowed to enter.

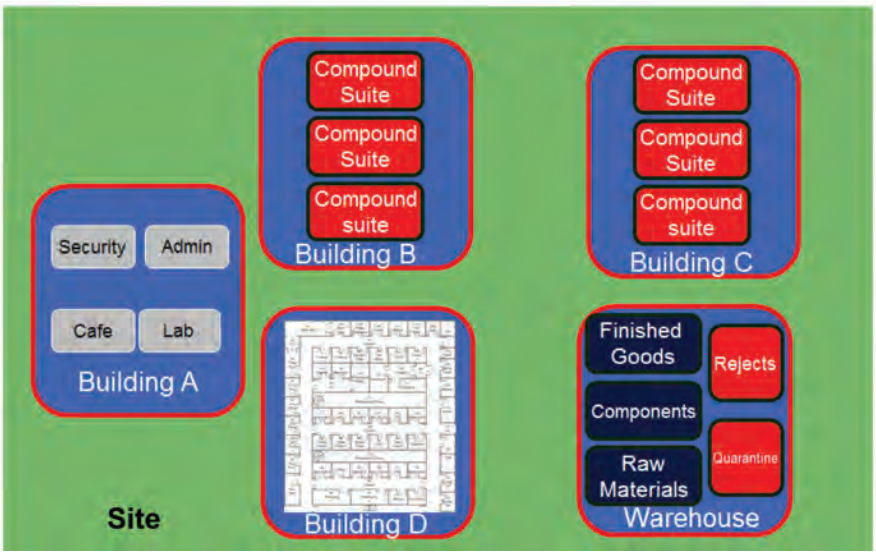

Figure 1. Typical site layout.

As such, the key is to assess the controls at the product boundary. ISPE's Risk-MaPP Baseline Guide is an important tool as it provides an approach to completing and documenting these assessments.

The risk of cross contamination from retention of residues after cleaning of shared equipment which is then available for carryover to the next product should be non existent as the regulations are clear that equipment should not be shared between beta lactam products and other products. Equipment between the different classes of beta lactams is also not to be shared. If existing equipment is to be re-used for either beta lactam products when previously used for other products or vice versa, a decontamination protocol should be developed and executed which contains quantifiable acceptance criteria intended to ensure that the risk of cross-contamination risk is compliantly managed. Accordingly, when reusing equipment that has previously processed beta lactams, an acceptance criteria should be established at a "no detect" level. It is also essential that the analytical methods be sufficiently sensitive. It should be noted that others have decontaminated equipment and even facilities with an analytical method sensitivity as low as 0.6 nanograms per cm^2.

Mechanical transfer is where residues on non-product contact surfaces are transferred to another product/process via equipment, materials, wastes and people transiting the facility. For example, residue on an employee's gowning could fall off the gowning into the next product's process if the gown is not changed. Clearly the best way to minimize mechanical transfer is to contain the compound/powders within the process. If the powder does not get out of the process, it is not available to get into another product/process. This is an area where many current facilities, which manufacture beta lactams, could use improvement. Many facilities dedicated to producing beta lactams do not consider the impact of open processing

and powder leakage/residues within the facility as a potential source of cross-contamination outside the facility via mechanical transfer. If a site is dedicated to manufacturing one of the classes of beta lactams, there may not be a cross-contamination concern; however, there may be an employee safety and environmental issue as employees may inadvertently transfer residues outside the site and even into their homes. An area to assess is the gowning. Is the gowning disposable? If so, is it disposed of in a manner, which limits mechanical transfer? Is the gowning reused and laundered? Is it laundered on site or off site? If it is laundered off site, how do you ensure that the laundry service is not mechanically transferring residues? Is it laundered separately? If you launder on site, do you have dedicated washers and dryers? If not, how does one ensure that there is no mechanical transfer from the laundering process? How do you control that it is laundered according to SOPs each time? Another area to assess is materials and wastes that are entering/exiting the processing facility. Are there residues on these items that could be mechanically transferred to other products or materials?

"simply following the requirements of the recent FDA Guidance to Industry on Non-Penicillin Beta Lactam Drugs is not enough to manage the risk of cross-contamination when these products are produced on sites that manufacture multiple products including more than one class of the beta lactams.

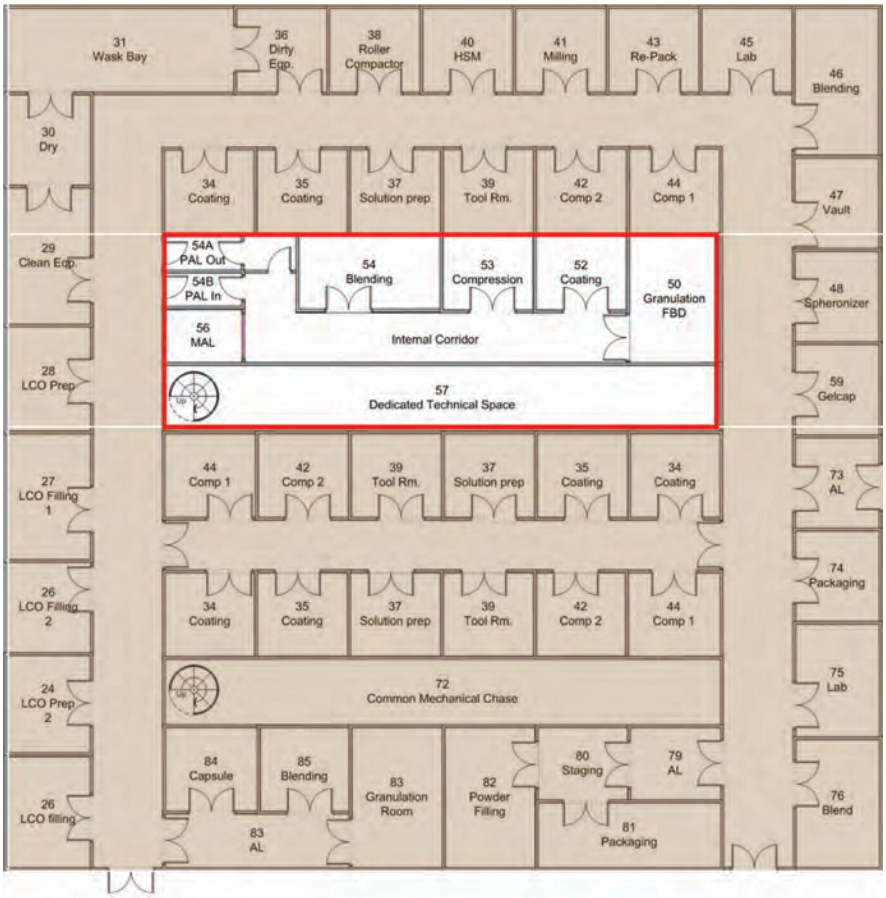

Figure 2. Dedicated and segregated suite within a multi-purpose facility.

Airborne transfer is where airborne particulate is transferred to another product/process either directly in air or by re-aerosolization of sedimented particulate. Similar to mechanical transfer, the best way to minimize airborne transfer is to contain the compound/powders within the process. When dealing with either a separate building or a segregated area in a multi-product site or building as the compound boundary an assessment of the incoming and exhaust air as well as the pressure gradient is needed to ensure the risk of cross contamination by the airborne route is controlled. The incoming air requires filtration. The most common approach is to filter the incoming air as well as the exhaust air. As these filters are considered critical controls for cross contamination control, they should be monitored.

Having controls in place to manage the risk of cross-contamination by any of the four modes is just one piece of the process. Routine performance monitoring is also required to ensure that the risk of cross-contamination continues to be managed to acceptable levels. There are various schools of thought on exactly what routine performance monitoring for the risk of cross-contamination entails. One idea is to provide monitoring which

should include alarms for all the controls that manage the risk such as:

- Electronic access control for mix-up
- Cleaning verification for retention
- Containment of closed systems for mechanical and air-borne transfer
- Pressure gradient for mechanical and airborne transfer
- Filter performance for airborne transfer
- SOP adherence for gowning, wipe down of materials/ equipment, mix-up, cleaning processes, filter change out, etc.

The other school is to routinely perform actual air sampling, swab sampling, and even surrogate/placebo testing to assess the operation of all the systems to manage the risk of cross-contamination. Whichever option is used, a justification is required as to why the chosen option is appropriate.

In conclusion, simply following the requirements of the recent FDA Guidance to Industry on Non-Penicillin Beta Lactam Drugs is not enough to manage the risk of cross-contamination when these products are produced on sites that manufacture multiple products including more than one class of the beta lactams. A risk assessment of all four modes of cross-contamination is necessary to show that the risk is being managed to acceptable levels. ISPE's Risk-MaPP Baseline® Guide is an essential tool for assessing the risk of cross-contamination.

About the Author

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Realizing Process Analytical Technology (PAT) in Process Development by Implementation of Near Infrared (NIR) Spectroscopy

by Michael Fowler, Janssen Vanderhooft, and Venkatesh Subramanyan

This case study demonstrates how using NIR spectroscopy in mix process development can shorten process development and scale-up timelines, accelerate time to market, enable generic products to include DoE, enhance the process knowledge, and optimize manufacturing processes for transdermal products.

For the last several years, the FDA has issued several guidance documents to encourage companies to implement components of Quality by Design (QbD) into various phases of product lifecycles with an emphasis on product development. Companies are expected to incorporate basic QbD elements in ANDA product filings starting in the year 2013. To guide companies in this endeavor, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has issued Q8(R2) Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System.[1-3] ICH Q8(R2) describes the scope and principles of QbD and suggests examples and methodologies to enhance product and process knowledge in formulation and process development; ICH Q9 provides guidance to implement quality risk management into product development by using scientific knowledge to make risk assessments; ICH Q10 provides guidance for using ICH Q8 and ICH Q9 principles in regulatory strategies. The FDA defines QbD as:

> *"A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."*[4]

In the guidance: *PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance,* the FDA recommends the use of Process Analytical Technology (PAT) as a tool to implement QbD methodology in product development.[5] **One way of utilizing PAT in development is by the use of near-infrared (NIR) spectroscopy. NIR Spectroscopy has been industry proven to be an effective PAT method because of relatively quick analysis times, non-destructive sample analysis, and no sample preparation requirement.**[6]

NIR spectroscopy is often utilized by companies to realize PAT with brand products in development and advanced stages of product lifecycles; however, NIR spectroscopy does not enjoy such widespread use in the generic industry due to a lack of resources or aggressive timelines. When the objective in developing a generic transdermal product is to demonstrate Qualitative (Q1) and Quantitative (Q2) equiva-

lence, development resources are often allocated heavily to process development instead of formulation development. This article discusses how NIR spectroscopy was used in the small scale development phase for a generic topical gel product and demonstrates how using NIR spectroscopy for mix process development can shorten overall development time and time to filing by minimizing the number of required experiments for process understanding, enable generic product development to include statistical design of experiments (DoE), enhance the resulting process knowledge, and optimize manufacturing processes.

Topical Gel Background

One critical activity common to most transdermal products is the development and optimization of mix processes for semi-solid, liquid solutions, gels, emulsions, and suspensions. Some Critical Quality Attributes (CQAs) for transdermal products at the mix stage are assay, content uniformity, viscosity, specific gravity, solvent content, and pH. Each of these CQAs has the potential to be monitored by PAT. Although NIR spectroscopy is capable of measuring many quality attributes, only content uniformity and viscosity were characterized in the study discussed in this study. To simplify the discussion of the mix process, any activity related to mixing, blending, homogenizing, or similar will simply be referred to as mixing.

Mix processes for topical gel emulsions and suspensions can be particularly challenging to develop.[7] Determining mix end points by visual examination is virtually impossible because products are often opaque; therefore, samples must be collected at discrete intervals for testing CQAs. In addition, the resources required to test these in-process samples make this approach less desirable. There are often mix stages between individual ingredient additions, further increasing the number of experiments that must be conducted to determine mix end points. PAT instrumentation allows these experiments to be conducted continuously, providing real-time feedback during the development mix process. The topical gel formulation for this study was comprised of typical components with common pharmaceutical functions, including solvents, Active Pharmaceutical Ingredients (APIs), preservatives, gelling agents, emulsifiers, and enhancers. A Bruker Optics, Inc. NIR Matrix-F spectrometer and probe was used for this study. A Charles Ross & Son Company 15 gallon stainless steel multiple-shaft mixer was used for gel mixing.

Topical Gel Mix and NIR Spectroscopy Process Description

The NIR probe generated spectra during the mixing process and analyzed the rate of change of functions such as the standard deviation over time to indicate gel content uniformity. Content uniformity was measured by a model-free, semi-quantitative approach – no model was generated prior to using the probe for the purpose of approximating content uniformity. Gel samples were physically taken periodically during mix trials from sections representing the top, middle, and bottom portions of the mixing vessel contents and submitted for analytical laboratory testing to confirm the real-time content uniformity results obtained from the NIR probe and to build a library of viscosity measurements for a subsequent mix. Content uniformity was measured by testing samples for content assay of the API and other components by HPLC. The viscosity was tested by a Brookfield viscometer. A viscosity prediction model was created using a Partial Least Squares (PLS) algorithm on viscosity data obtained from an initial trial run for subsequent trials and process optimization.

Early mix process development for the gel was performed without NIR spectroscopy through a series of trials executed to study the order of addition, process temperatures, mix blade shear rates, and mix times. These trials resulted in a process that produced a gel with the appropriate physical and chemical properties. Numerous single factor lab-scale mix trials were performed to investigate the suitability of a dual-shaft mixer, order of addition, and gain early process understanding.

Small scale mix trials were performed based on the results of the lab scale trials. Scale up was performed on equipment with geometric similarities and the same mix blade tip speeds as those used on the larger scale. Adequate process understanding was obtained for the gel mix process such that the process was scaled with ease to a commercial size dual-shaft mixer with anchor and high shear disperser blades. The Critical Process Parameters (CPPs) identified during process development were blade speeds, addition times of several components, and inter-step and final mix times.

To demonstrate the utilization of NIR spectroscopy in process optimization for a topical gel, three trial mixes were performed. To simplify the discussion of the mix process and to demonstrate the NIR probe capabilities, the gel mix process was divided into five stages:

Stage 1: Addition of solvents and preservatives
Stage 2: Addition of emulsifiers, humectants, and surfactants
Stage 3: Addition of gelling agent
Stage 4: Addition of API
Stage 5: Addition of pH adjustment

An NIR probe in stainless steel housing was attached to the small scale mixer through a porthole on the mixer lid. Initial individual spectra of each component to be charged into the mix vessel were collected by dipping the probe in small aliquots of each component. The spectra were saved to create a library for performing process analytics, such as content uniformity during mixing and generating prediction models for subsequent mixes.

The first trial mix was performed by following a previously established mix process as an experimental control for blade speeds and mix times. During a typical gel mix, inter-stage mix intervals exist to ensure content uniformity before proceeding to the next stage. Content uniformity data was collected with the NIR probe during this trial to demonstrate the probe capabilities and to identify which inter-stage time intervals could be decreased for future trials. Step-wise viscosity data was collected during the trial to build a prediction model for the subsequent second and third trial mixes.

Unlike the first trial mix, the second and third trial mixes were performed using NIR spectroscopy as the primary indication of content uniformity rather than using the specified mix time ranges from the control process. After each addition step, the cumulative mix spectrum was monitored in real-time. Once the slope of the spectrum graphically approached zero, the mix contents were assumed to be mixing at steady state and ready for the next addition step.

For consideration, the curve in Figure 1 shows the cumulative mix spectrum for content uniformity during and immediately after the stage 2 component addition and is representative of the stages of the mix. The vertical axis is the measure of change of content uniformity and the horizontal axis is the time in seconds of the mix step. The addition of the components is evidenced by the relatively high percentage changes of the Relative Standard Deviation (RSD) of the mix spectrum. RSD in this example is a measure of change and therefore is an indication of the amount of change occurring in the mix; large differences in RSD values correspond to significant change, or lack of content uniformity of the mix contents. Inversely, low RSD values or visibly flat sections (zero slopes) of the curve represent steady state mixing.

Results and Discussion

The analytical test results confirmed that the topical gel was in fact well mixed when NIR spectroscopy indicated steady state mixing by displaying visibly flat sections of the curve (zero slopes). Once it was confirmed that analysis of the spectra slope may be used as an indicator of content uniformity, the control process was compared to the three mixes performed with NIR spectroscopy to calculate potential time savings compared to the control process. For the purposes of comparing this mix process with and without NIR spectroscopy, the inter-stage mix time at stages 3 and 5 were not compared to the control process because these stages depend on mix scale. While mixes with the NIR probe were executed on small scale equipment, the control process is a large scale process. Table A is a summary

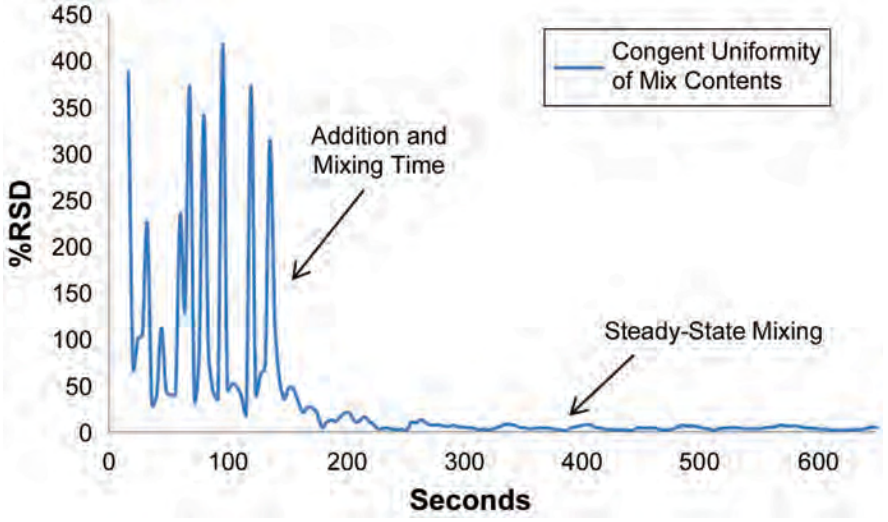

Figure 1. Cumulative mix spectrum for content uniformity of stage 2 addition.

of the mix time comparisons.

The first trial mix was performed to gather homogeneity and viscosity data and to verify these quality attributes by laboratory testing. The primary objective of the second mix was to utilize the viscosity prediction model to predict viscosity. The primary objective of the third mix was to optimize mix time, a critical process parameter. For all three mixes, samples were submitted for laboratory testing to confirm acceptable content uniformity ranges, a critical quality attribute. The cumulative mix time of the isolated stages of the control mix process was 75 minutes. The cumulative mix times of the same stages in the mixes with the NIR probe were 61, 43, and 31 minutes, respectively. The third mix showed that it is possible to shorten the process time by 60% compared to the control.

Stage	Control Process	Mix #1	Mix #2	Mix #3
Stage 1	30 mins	21 mins	15 mins	22 mins
Stage 2	30 mins	28 mins	17 mins	4 mins
Stage 4	15 mins	12 mins	11 mins	5 mins
Cumulative Mix Time	75 mins	61 mins	43 mins	31 mins
% of Control Mix Time	N/A	81%	57%	41%
Viscosity (cP)	N/A	1,435	~1,485	N/A

Table A. Inter-stage time comparison of mixes to control process.

The viscosity from the control process was not included in this comparison because viscosity is measured using a different laboratory method than was used for the mixes in this comparison. The first mix was performed using the same blade speeds and mix times as the control process, the viscosity data from the first mix is representative of a proper control. The viscosity samples submitted from the first mix were used to generate a prediction model using PLS which accurately predicted the viscosity in the second mix to within 50 cP (1,435 vs. 1,485 cP). It is noteworthy that only four samples were required to generate the viscosity prediction model.

Quantitative Statistical Analysis

The ability to create predictive models for mix quality attributes is valuable for multiple stages of PQLI, most notably when identical processes are repeated or similar products will be manufactured repeatedly. A model-free approach to monitor a quality attribute such as content uniformity, however, is especially useful in the development phase of PQLI. Consider a DoE for a mix process with three addition steps (e.g., solvent, API, gelling agent) and four process parameters (anchor and disperser blade speeds, API mix time, and final mix time). To simplify the experiment, the investigator has prior knowledge that the API and gelling agent can be added directly to the solvent without a specified addition rate, but that a mix time is required before adding the gelling agent. Table B shows the example mix process and process parameters.

One possible DoE to optimize this process would assign the blade speeds as 2-level categorical factors and the mix times as continuous factors with a time range. The objective of the experiment would be to manufacture product with acceptable CQAs in the most efficient time and enhance product and process understanding through investigation of main and interaction effects of the CPPs, criticality rankings, and linking CQAs to CPPs. To accomplish this objective, a screening design and subsequent augmentation, an I-Optimal, or equivalent design could be performed. For example, an I-Optimal design approach, given a signal-to-noise (S/N) ratio of 2.0 and a minimum experimental power of 0.80, would require that 13 runs be performed; however, the number decreases almost 50% to seven required trial runs if the investigator utilizes NIR spectroscopy to eliminate mix time as a factor in the experimental design. The type of designs, number of experiment runs, and other activities of product development performed by a company should be "based on sound science and quality risk management" according to the risk profile of the developing company. For example, other methods of decreasing the number of runs in a DoE may include increasing the S/N ratio, decreasing the power of experiment, performing lab-scale trials, and use of prior knowledge.

Conclusion

This case study demonstrates how PAT and NIR spectroscopy in particular, may be used to define CQAs and CPPs for mix processes of generic transdermal products. Specifically, NIR spectroscopy was used in this case study to implement PAT on a mix process to analyze content uniformity with a model-free approach and viscosity with a quantitative model. NIR spectroscopy may be used to develop quantitative prediction models methods for analysis of other physical and chemical attributes including assay, pH, and specific

Mix Step	Anchor Blade	Disperser Blade	Mix Time
1. Add Solvent	Two levels: Slow and Fast	Two levels: Slow and Fast	N/A
2. Add API			API Mix
3. Add Gelling Agent			Final Mix

Table B. Example mix process and process parameters.

gravity. Although most attributes require method development, content uniformity is model-free and requires no prior runs. DoEs designed with NIR spectroscopy and other PAT tools will enhance product and process knowledge, decrease the number of required runs for process optimization, and enable companies to incorporate elements of QbD into regulatory filings.

In summary, this case study demonstrates how an approach of using model-free and quantitative analyses with NIR spectroscopy in mix process development can shorten process development and scale-up timelines, accelerate time to market, enable generic products to include statistical design of experiments (DoE), enhance the product and process knowledge, and optimize manufacturing processes for transdermal products.

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Choosing the Optimal Hygienic Seal for Enhanced Process Performance

by Robert Dubiel and James D. Vogel, PE

This article presents how seals used in hygienic clamp fittings, diaphragm valves, and O-rings are integral to process performance, preventing leaks and contamination.

Seals are integral to process performance and used throughout the biopharmaceutical, pharmaceutical, and food industries, primarily in hygienic clamp fittings, diaphragm valves, and O-rings. They maintain the integrity of the process and seal it from outside conditions to prevent leaks and contamination.

Current biopharmaceutical processes usually require one or more Steam-In-Place (SIP) cycles per production batch. Depending on the requirements and the location in the process, the number of SIP exposures that a seal may be subjected to may be as high as 20 to 30 SIPs per production batch. In addition, automated Clean-In-Place (CIP) operations are more commonplace today. One cleaning per production batch is typically required, and cleaning cycles usually consist of weak caustic acid and/or bleach solutions at elevated temperatures. This is in sharp contrast to the food industry, where most processes undergo less aggressive sanitization and cleaning cycles.

State of the Industry

The business climate is changing in the biopharmaceutical industry. Trends are shifting to contract manufacturing, higher plant throughputs, reduced plant down time, and increased focus on cost-of-goods-sold, while also maintaining a strict sense of quality. Biopharmaceutical manufacturing must be in compliance with current Good Manufacturing Practices (cGMPs), and the process design needs to provide process reproducibility, as well as ensure product stability and purity. Process modifications are allowed only if it can be proven that the resulting final products are similar in terms of quality, safety, and efficacy.

In response to these industry trends, the United States Food and Drug Administration (FDA) issued the "Pharmaceutical cGMPs for the 21st Century" initiative in 2002. Included in this landmark initiative is a risk-based approach to manufacturing science. This approach employs many of the initiatives which the *International Conference on Harmonization (ICH)* has issued in its document, Q9, *Quality Risk Management*.

Risk is usually defined as the probability of harm multiplied by the severity of harm. Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes. Risk knowledge means more focus on the most critical aspects of the process and more rigorous application of process development, technology transfer, monitoring, and control.

The intent of this initiative is to encourage early adoption of new technological advances by the pharmaceutical industry. The *Office of New Drug Chemistry (ONDC)*, within the *Center for Drug Evaluation and Research (CDER)*, has established a risk-based pharmaceutical quality assessment system to replace its *Chemical Manufacturing and Controls (CMC)* review system. It focuses on critical pharmaceutical quality attributes and their relevance to safety and efficacy. The strategy is based on the reflection of the manufacturer's

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...am, broken down and is finding it's way into your product.

FlowSmart's EPDM still looks new after one year of use. This is the same EPDM compound that we've used for a decade.

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FlowSmart In-house technology includes: Extruding, Braiding, Calendaring, Compression Molding, Injection Molding, Hose Wrapping, Milling. 3 cleanrooms.

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	FlowSmart	Brand X	Brand Y	Brand Z
Produces Gaskets in an ISO 7 Cleanroom	YES	NO	NO	NO
EPDM Gaskets like new after 1 year in a biotech process	YES	YES (see 1)	NO	NO
Has 1, 2 or 3 ISO cleanrooms	3	0	0	0
Produces Platinum Silicone Tubing in a cleanroom	YES	NO	NO	NO
Produces Platinum Silicone Hose in a cleanroom	YES	NO	NO	NO
Packaged in an ISO 7 Cleanroom	YES	NO	NO	NO
In-house Extruding, Braiding, Calendaring, Compression Molding, Injection Molding, Hose Wrapping, Milling.	YES	NO	NO	NO
Produces only high purity polymer products	YES	NO (see 2)	NO	YES

1 Product has tested to also look new after a year.
2 Primarily an industrial producer. High purity products are only a small fraction of their business.

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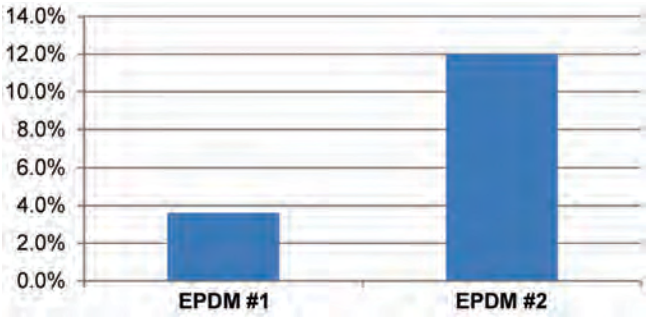

Figure 1. Compression set after 22-hrs at 100ºC comparing 70-durometer EPDM compounds.

understanding of manufacturing process, process control, and quality systems. The FDA's Aseptic Processing Guidance underscores the advantages that automation and isolation concepts offer in protecting the exposed sterile drug product during its aseptic manufacture. It advocates a risk-based and quality system framework that stresses contamination prevention.

Materials Science of Seals

In order to prevent contamination in a product, it is important that the materials being used in the process are well understood. There is an assumption by many that however one material performs, all others will perform equally. This is definitely not the case. Figure 1 shows two different USP Class VI 70-durometer Ethylene Propylene Diene Monomer (EPDM) compounds from the same manufacturer. While both compounds have very similar original properties, there is a significant difference in the compression set of each material after only 22 hours in 100°C air. This difference can be caused by the specific polymer used, the types of filler used, or the type and amount of curative. This simple material property – the compression set – can be a good surrogate of how much sealing force is retained by the gasket over a period of time, which is important information to understand for a sanitary gasket. The greater the compression set, the less sealing force retention on the gasket and the more likely the end user is going to have to re-torque the clamp to regenerate a seal. Understanding properties such as compression set, Compressive Stress Relaxation (CSR), and fluid resistance can be critical to understanding just how that specific compound will perform in an application.

Figure 2. Various EPDM products.

Another important factor to consider is the pedigree of the ingredients used to create the material. Many industries – such as the automotive industry – already require gasket suppliers to submit documentation for any ingredient changes and even mixing location changes due to the potential differences that can be created in the performance of the end product. This has become all the more important the past several years as changes in the overall global economy have forced raw polymer suppliers to consolidate their facilities, eliminate certain polymer grades, and create new polymer grades to meet the demands of the various industries. Having an understanding of the gasket source and what they are supplying is becoming more critical for each end user.

Finally, it is important to understand that materials are used across multiple industries and specifying a USP Class VI material may not necessarily be the only thing an end user needs to know. EPDM materials are used in products such as automotive door seal extrusions and grommets, as well as pharmaceutical sanitary gaskets – some examples are shown in Figure 2. This is why it is critical to have an understanding of the material being used. For optimal long-term performance of a system, the end user also should have an understanding that the EPDM being received today is the same material that was received the day before, and will be the same material received tomorrow. With the appropriate traceability in place, the end user can be assured that the material utilizes the same polymer, same fillers, and same formulation along with mixing method, from part to part.

Evaluating Seals and Seal Performance

The adoption of advanced sealing technologies has lagged behind the progress of the biopharmaceutical industry. The industry has applied standards from other related industries, like the 3A and *European Hygienic Engineering and Design Group (EHEDG)* standards, where appropriate. However, materials of construction are becoming more and more sophisticated. New materials of construction have been introduced, such as fluoroelastomer (FKM) and perfluorinated elastomers (FFKM), and each has been met with some limited success. Specific concepts like compression control design enhancements, PTFE-enveloped elastomers, and stainless steel and glass mixed with polytetrafluoroethylene (PTFE) also have been introduced to the industry, also with limited success.

The *American Society of Mechanical Engineers (ASME)* has provided a standard to the biopharmaceutical industry with the publication of the *ASME BioProcessing Equipment Standard (BPE)* in 1997. The BPE Standard addresses the requirements of the bioprocessing, pharmaceutical, and personal care product industries, as well as other applications with relatively high levels of hygienic requirements. The

standard covers, directly or indirectly, the subjects of materials, design, fabrication, pressure systems (vessels and piping), examination, inspection, testing, and certification. It is a consensus standard which is internationally recognized and contains a specific section on sealing components (formerly Equipment Seals), Part SG. Specific seal requirements include:

- User design requirements to ensure sterilizability and cleanability, e.g., seal leakage and hygienic seal intrusion
- Materials of construction requirements to minimize the interaction with the process, e.g., biocompatibility, process compatibility, surface finish, particle generation, and extractables
- Compliance requirements to ensure proper testing and supply chain management, e.g., Certificate of Compliance, packaging and storage recommendations, and test requirements

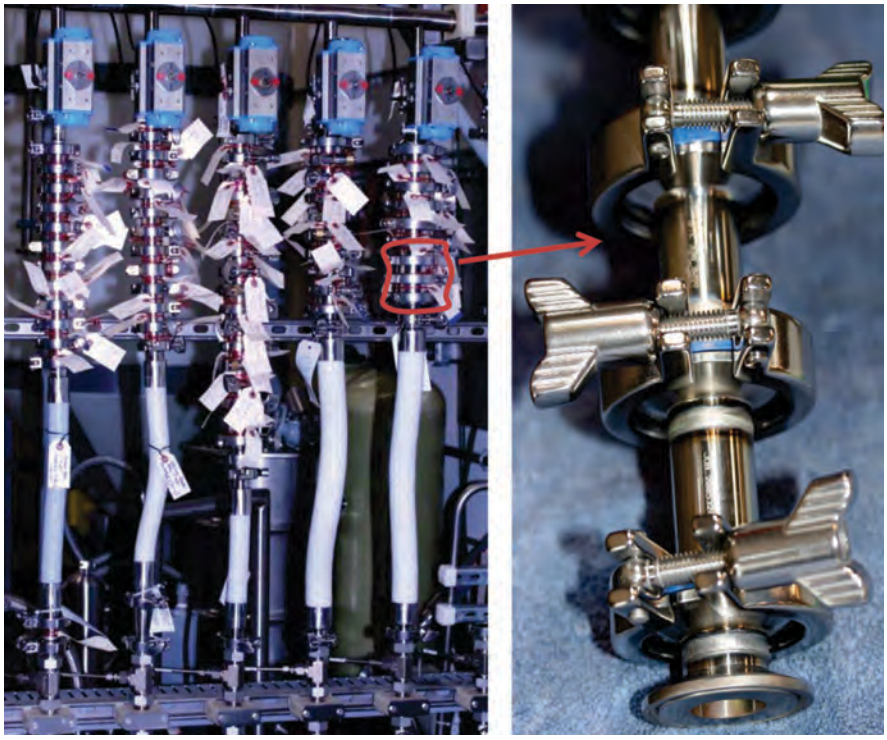

Figure 3. Sample bench test (photos courtesy of The BioProcess Institute).

The BPE Standard addresses the need to characterize seal performance with the establishment of the Standard Process Test Conditions. This non-mandatory appendix outlines standard test conditions to simulate typical biopharmaceutical SIP and CIP cycles. It recommends acceptance criteria for hygienic seals and levels of performance for classification. An acceptable seal is one which will maintain pressure without leakage, have minimum levels of intrusion into the flow path, and appear relatively unchanged and free of defects after exposure to process cycles. Testing can provide the end user much needed information as to the overall performance characteristics of the gasket design and material. But the importance of bench testing goes beyond just gaining some understanding of a gasket and its design – it also can be used as a qualification for use in an end user's system.

In the BPE Standard, there already exists a test procedure for standard process testing sanitary gaskets.[1] While this procedure may not prove that a particular gasket will work for some specified period of time in a given system, it can be used as a baseline for determining how one gasket will perform when compared with another. Variations of this test also could be set up by the end user as a means of qualification for use in one's own facilities. Figure 3 provides an example of a bench test setup with multiple gaskets installed in series. The results of a 500 SIP exposure test showed virtually no physical difference between the gaskets shown in Figure 4 after exposure to 10, 100, and 500 SIP cycles. In addition, the gaskets shown in Figure 4 were able to maintain sealability throughout the test without requiring any re-torque throughout the 500 SIP cycles.

Other industries, such as automotive, have been using bench testing of gaskets for many years as a means of qualifying new designs. In order for a gasket supplier to provide a particular product in a particular application, the gasket supplier will not only have to gain a material approval, but also will need to prove that the design passes the approved bench test before the supplier can provide the product. The pharmaceutical, food, beverage, and dairy industries have

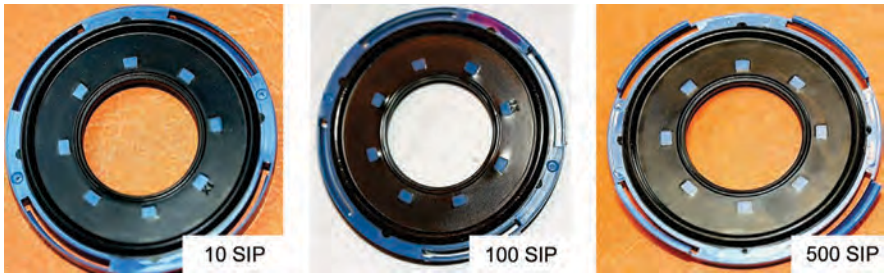

Figure 4. EPDM gasket over 10-100-500 SIP cycles exposure (photos courtesy of The BioProcess Institute).

"Developing a standard bench test procedure and having an approved source could pay dividends for an end user in the long term.

the opportunity to apply the same principles to improve the overall quality of the gaskets they receive. Using the ASME BPE Standard, end users can add this test (or something similar) to their approval requirements before gasket suppliers can introduce a new product. Furthermore, since many end users lack the time and resources to conduct gasket testing continuously, they can provide a list of approved test sources for the gasket suppliers to use. In this way, the end user has only to focus on auditing the testing facility for compliance with their approved procedure. This process will help prevent receipt of unapproved gaskets. Gasket testing will reveal varied performance of different types of gaskets and gaskets from different manufacturers, displaying "worst" to "best," as shown in Figure 5. This can help the end user determine the timing between maintenance schedules and gasket replacement.

Developing a standard bench test procedure and having an approved source could pay dividends for an end user in the long term. While it is very difficult to develop the most accurate bench test that meets all of the end user's needs, once a bench test has been standardized, continuous improvement on that procedure can take place and eventually a test can exist that will help the end user better predict maintenance intervals for various gaskets.

A Risk-Based Approach to Better Seal Performance

As stated in the cGMPs, the biopharmaceutical industry must ensure its product quality, safety, and efficacy are the same or better when it makes any process change. Historically, there have been barriers to adopting new developments in seal technology into cGMP processes. Seal suppliers have not always provided robust, transparent compliance and quality assurance practices. At the same time, end users have not always properly considered cost-of-ownership models that take into consideration all potential costs. These costs include installation, routine maintenance, and non-routine deviations, not just the initial cost of the seal itself. In addition, both seal suppliers and end users have sometimes lacked effective performance testing to assess the seal's fitness-for-use and potential cycle life.

By employing a risk-based approach to assessing the performance of seals, the biopharmaceutical industry can overcome these barriers and easily enhance their process performance by implementing the proper seal selection process.

Specifically, in the evaluation of a potential replacement seal, the following should be evaluated:

- Seal Supply Chain:
  - Manufacturer
  - Distributors
  - Quality Assurance
  - Supply Chain Integrity
- Process Application
- Installation
- Retooling
- Procedure Changes
  - Process Performance (Fitness-for-Use)
  - Maintenance (Life Cycle)
  - Potential for Failure

The decision to change a seal can be clouded with many concerns, such as lack of knowledge of materials and their performance, unclear vendor qualifications, and arduous change control processes. Combined, these become barriers to change and are not always consistent with the cGMPs and the quest to ensure quality, safety, and efficacy. Process performance and proper assessment of risk must drive this evaluation.

Figure 5. A range of gasket performance after 500 SIP cycles exposure (photos courtesy of The BioProcess Institute).

Costs are the next consideration when contemplating any change. Challenges include increased cost control, desire for improved up-time of equipment, and getting the most out of the capital equipment each company already owns. Understanding all of the associated costs with the seals in a system, and not just the initial cost of the seal itself, is important if one is to truly reduce overall costs and improve equipment up-time.

One example that demonstrates this point is a typical Water for Injection

Number of Connections	100
Avg. Time to Replace a Gasket	24 minutes
Avg. Time to Re-Torque a Gasket	4.8 minutes

Table A. Maintenance on sanitary fittings.

(WFI) system used in a pharmaceutical facility. The WFI systems are fundamental to the manufacture of a pharmaceutical product. WFI systems are used for cleaning and rinsing, and can be the last thing a piece of process equipment sees before the product is introduced. Water can be a source of bacterial endotoxins and other toxic contaminants that could render a cell culture operation ineffective within a facility, so the WFI system and the components used within it can be a cause for batch failures and the associated costs. A typical WFI system is often found in hard-to-reach locations, such as the facility ceiling or wall. Based upon actual experience with WFI systems, an average of 24 minutes is required to replace a gasket, due to a variety of factors. The fittings are often not easily accessible, requiring time to assess the best course of remediation, followed by potential removal of insulation, pipe supports, sensors, and other lines. Larger lines may require more than one person or special apparatus for removal, and pipe misalignment may require additional remediation efforts. As a result, it is a system for which long-lasting gaskets are desired. A typical WFI system can utilize approximately 100 fittings, and for those 100 fittings, it can take "five man-days" to replace the gaskets. A "man-day" is the number of days it takes a person to accomplish the task. Five man-days can take one person five days to finish the task, or it can take five people one day to complete the task. Having to re-torque the fittings throughout the system can take "one man-day." Based on this information, the assumptions for maintenance on the sanitary fittings can be seen in Table A.

Assuming a standard all-EPDM gasket might last up to 12 months, with each fitting requiring a re-torque once every three months, the costs for the associated maintenance of

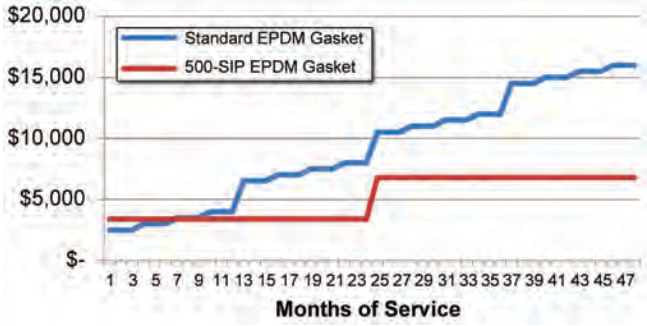

Figure 6. Gasket maintenance costs over time (typical WFI system).

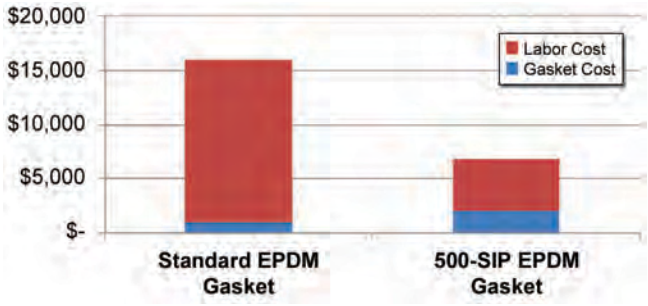

Figure 7. Estimated cost breakdown over 48-month period.

that system can be calculated. Using these assumptions, the cumulative costs associated with maintaining the gaskets on a typical WFI system are shown in Figure 6. While using a standard all-EPDM gasket may save the end user on costs associated up-front based solely on gasket cost, it could end up costing the end user more within a 12-month period when compared with a gasket capable of sealing for a two-year period without need for re-torque – even if the end user were to pay ten times as much for the gasket.

Often, end users look at the price for each gasket rather than taking a look at the overall costs associated with maintaining the system. Looking at the breakdown of associated costs shown in Figure 7, one can tell the greatest portion of the cost associated with maintaining the seal in a WFI system is in the labor – not the gasket. Based on this, the focus should be on reducing the labor associated with changing the gaskets over the cost of the gasket itself.

Finally, one must understand the potential for failure. Simply put – a seal failure is unacceptable. The purpose of the seal is to separate the process from the environment. Failure to do so can compromise the integrity of the process and expose the process and patient to unacceptable risk. The costs associated with those failures can be significant, as shown in Figure 8. This is not to mention the risk to the quality, safety, and efficacy of the end product itself.

Having a solid understanding of the supply chain and quality assurance with the associated seals in a process can

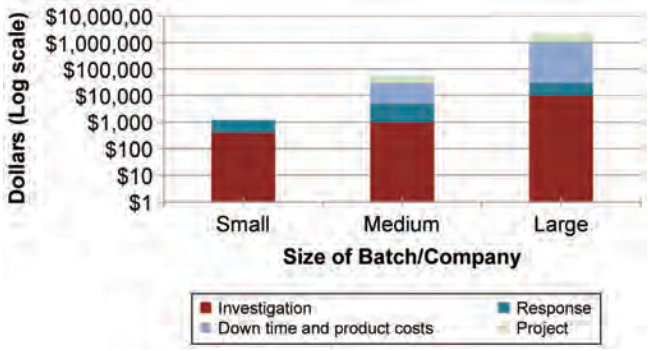

Figure 8. Costs of a seal failure (Vogel, 2010).

help prevent batch failures from occurring, or at the very least, expedite the corrective action process to determine the true root cause of the failure so that permanent corrective action can be instituted to prevent recurrence of the issue.

> *"A better performing seal results in a more robust process, which delivers a more consistent drug substance.*

Conclusion

A better performing seal results in a more robust process, which delivers a more consistent drug substance. It provides reduced risk to the biopharmaceutical manufacturer, is in better compliance with current Good Manufacturing Practices (cGMPs), and provides better process reproducibility to further ensure future product stability and purity. At the same time, a better performing seal also can help the biopharmaceutical manufacturer achieve a cost savings of thousands of dollars annually and can prevent many times more that amount in nonconformance events, their investigations, and their corrective and preventative actions.

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PHARMACEUTICAL ENGINEERING Interviews

Julie Kim, Global Franchise Head of BioTherapeutics, Baxter International, Inc.

Julie Kim is the General Manager for the global franchise, the BioTherapeutics Franchise, which includes a portfolio of antibody-replacement therapies, albumin, and a number of specialty plasma proteins that are available globally. Kim began her career in the strategy function in 2001 on key issues across the BioScience division. Over the next 10 years, she advanced through positions of increasing responsibility within BioScience in market development in emerging geographies and global marketing roles. Prior to joining Baxter, Kim worked in healthcare consulting for more than seven years. In addition, Kim is passionate about corporate sustainability and diversity and inclusion. She sits on the Baxter Sustainability Steering Committee, the BioScience Diversity and Inclusion Committee and is an advisor for multiple Business Resource Groups.

What are your responsibilities in your current role as Global Franchise Head of BioTherapeutics?

I am responsible for managing the global business, including setting the commercial, R&D and manufacturing direction for the franchise. It also includes oversight of the Covington facility.

What experiences prepared you for your current position?

Throughout my career, I've had very diverse experiences with exposure to a variety of companies and roles in different functions and geographies.

You played a lead role in bringing a state-of-the-art manufacturing facility to Covington, Georgia. Tell us about that project and your involvement.

We were tasked with identifying the best location for a greenfield facility and we worked with Deloitte Consulting on the process. My role initially was to bring the commercial perspective to the project and I eventually became responsible for the project overall.

In a nutshell, what was the business case to build such a facility?

The Covington facility is needed to support the growth of the BioTherapeutics franchise, which is a multi-billion dollar global business with a strong growth trajectory. The existing manufacturing footprint is not sufficient to sustain future growth.

What are some of the biggest business risks associated with building a large state-of-the-art biomanufacturing facility?

Many of the risks are related to the long time it takes to build and approve such a large, complex facility in the

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plasma protein industry. A couple of the biggest risks are: 1) being able to accurately anticipate product supply and demand many years in the future; and 2) staying current with continuously evolving industry technology and regulatory compliance expectations. The manufacturing processes used to produce plasma proteins are very specific and cannot be easily reconfigured to make other biopharmaceutical products if product demand does not materialize. Of course, there are many other risks associated with a greenfield project of this magnitude including hiring and training qualified staff at a high rate, coordinating the work of multiple contractors and consultants to ensure timely completion, and developing the organization infrastructure.

What factors do you believe contributed most to Baxter's success and growth in the biotechnology industry?

Baxter's leadership in the biotechnology industry began in 1953. Over the decades, we have continued to invest in innovative science, allowing us to reach more patients across more disease areas. The breadth and depth of our expertise in recombinant protein manufacturing and plasma fractionation technologies continue to set us apart. Today, Baxter is a leading producer of both plasma-based and recombinant clotting factors for hemophilia, as well as biopharmaceuticals used to treat immune deficiencies and other blood-related disorders.

The facility of the future is said to be one that has different facility attributes than the traditional stainless-steel basis. Flexibility, diverse product mixes, rapid product development, increased reliance on closed system design and operational requirements will become drivers of facility design. How does this apply to the new Covington, GA site?

The Covington facility will be more vertically integrated than any of our other sites. It will combine new technologies and the "best demonstrated practices" from our other plants on one site. We are adopting single-use technologies where appropriate to reduce contamination risk, improve operating costs and efficiencies. The latest and emerging trends in GMP (environmental and viral) controls are being incorporated in the facility design. We think this facility will also provide a more employee-friendly environment than the typical pharmaceutical plant such as bringing significant natural light into the manufacturing areas through window walls and skylights. The plant has been designed with future expansion in mind. Nearly all functions and operations on the site can be significantly expanded with minimal disruption to ongoing operations. We will also deploy a high degree of automation – process controls, building systems, and documentation management – throughout the facility.

What significant changes have you seen that impact the development, engineering, manufacturing, and business areas in the biotechnology industry in the last few years? What changes do you anticipate in the next few years in the biotechnology manufacturing market?

Heightened emphasis on facility and process GMP design regardless of a company's quality record with existing processes.

Why did you accept the invitation from ISPE to present at our 2013 Annual Meeting?

I accepted the invitation in order to share the experience we continue to build on from our 60-year legacy of developing and manufacturing life-saving and life-sustaining biotherapeutic products. The products and therapies Baxter's BioScience organization produces are varied, but they share the common connection of improving the lives of patients with rare conditions, chronic diseases or limited treatment options. It takes tremendous financial, time, and resource commitments to expand the supply necessary to keep pace with the anticipated demand for these critical therapies.

ISPE is a tremendous resource for staying current with the latest technology and regulatory trends in the global pharmaceutical manufacturing industry.

What will be the focus of your presentation?

The focus of my presentation will be on "why" Baxter is expanding capacity around the globe to address plasma-derived therapies. The other ISPE Annual session will address "what" we are building in Covington, Georgia to achieve this end!

How can organizations such as ISPE contribute to the biotechnology industry?

ISPE is a tremendous resource for staying current with the latest technology and regulatory trends in the global pharmaceutical manufacturing industry. When a company is investing more than a $1 billion over five years to bring a new greenfield facility on-line it is critical that emerging trends are anticipated and incorporated in the design, construction, and operation of the facility.

2013 ISPE Annual Meeting – Your Competitive Advantage

A message from the ISPE Annual Meeting Chairman, Bob Chew

Every decision ever made by any manager involves an element of risk management. What technology to employ? Is it proven? Will it reduce manufacturing problems? Should process development be given more time? How can I best meet compliance requirements, assure quality, and maximize production throughput? How large should the project team be, and who should be responsible for what? How much do I invest in a quality build in order to reduce schedule risk, but within budget parameters? What are best practices, and what resources are available to manage risks to the supply chain? How will local government regulations concerning environmental, labor, and GMPs impact my project?

They say knowledge is power, but knowledge is basic to successful risk management and decision-making. What are your sources for knowledge? Colleagues? Internal company sources (and where do they come from)? Journals? Internet? What is the genesis of innovation – at least with respect to GMP-regulated manufacturing? Not just new molecules, or the latest automation technology, but innovation with respect to project delivery, quality systems, supply chain assurance...the list goes on. Are your ideas innovative? Where do you find inspiration for innovation?

The 2013 ISPE Annual Meeting offers a multitude of opportunities for discovery: insightful presentations, thought-provoking new approaches, case studies, vendor exhibits, networking with colleagues, regulatory forums, executive symposia. This year's Annual Meeting, to be held November 3 to 6 in Washington, DC offers these opportunities and more, giving you the added knowledge to be more impactful in your job or to help advance your career in a new direction.

> *"The 2013 ISPE Annual Meeting offers a multitude of opportunities for discovery: insightful presentations, thought-provoking new approaches, case studies, vendor exhibits, networking with colleagues, regulatory forums, executive symposia.*

Years ago, I was part of ISPE's Education Committee, which was charged with producing the Annual Meeting. Last year, and again this year, I have had the honor of chairing ISPE's Annual Meeting Committee. I cannot recall a year where there was a better lineup of subjects and speakers than this year, and I want to thank the committee personnel for their perseverance and professionalism in making this program come together.

The Annual Meeting will feature the following tracks:

- Executive Series
- Global Regulatory Summit
- Manufacturing Technology
- Manufacturing Facilities and Design
- Investigational Products
- Information Systems
- Global Regulatory and Compliance
- Global Drug Supply
- Project Management
- Quality Systems
- Young Professionals

So whether you are managing production, technology, people, or projects or whether you are a young professional or a grey-hair like me, this year's Annual Meeting has something for you,

Let's start with the Executive Series. Topics will include a case study of the team design effort for the new Baxter manufacturing campus being built in Georgia. Several regulatory related presentations will address quality metrics (with FDA conversations) and ICH Q10, Pharmaceutical Quality Systems. Other subjects will include continuous manufacturing and facilities of the future.

Concludes on page 112.

Getting FDA Approval for Breakthrough Therapies

"The new timeline doesn't mean doing less, it means doing more sooner."

The U.S. Food and Drug Administration's existing expedited pathways to approval of new drugs – Accelerated, Fast Track, and Priority Review – are already challenging. But, despite these tracks, the FDA was perceived as often moving too slowly, according to Earl Dye, Director, Genentech, Inc. USA. Now, the FDA's new pathway for accelerated development of "breakthrough therapies," authorized by the 2012 legislation known as *The Advancing Breakthrough Therapies for Patients Act*, part of the 2012 FDA Safety and Innovation Act (FDASIA), will greatly accelerate the approval process of breakthrough therapies.

The innovative program comes with new and different challenges as well as opportunities. The challenges to having a new, breakthrough drug product gain early approval become apparent when the FDA uses defining phrases such as "the drug must demonstrate clinical evidence of being a substantial improvement over existing therapies," it must "meet unmet medical needs," and the therapy must be able to "treat a serious or life threatening disease."

Many firms think they have just such breakthrough products waiting in the wings and are eager to get them into and out of the shorter pipeline and on the way to commercialization.

Although the program has only been in existence since October 2012, the requests for early approval on breakthrough therapies are coming in "fast and furious," according to David Doleski, Director FDA/CDER, Office of Compliance. He says that the FDA is currently working on providing guidance and direction to companies seeking quicker approval, and adds that the FDA is committed to a 60 day window to grant or deny requests.

"Requests are coming in at the rate of probably two or three per week," says Doleski. "As of May 23, we have received 51 breakthrough designation requests and 20 have been granted. Eight of the 20 are for oncology drugs and 12 of the 20 are for non-oncology drugs. Downstream, there is going to be a lot of work to be done."

The key to the pathway for breakthrough drug approval is clinical data showing that a new drug will be "game changer," Dye adds, adding that there will be "challenges and benefits" from production to launch.

"Overcoming these challenges will require frequent and interactive communication between sponsors and the review team throughout drug development, "explains Dye. "Senior managers and experienced review staff will have to be very collaborative. The overall benefit is that time to launch may be cut by two-thirds and the path to approval – one that previously took seven to 10 years to complete – may only take three to five years. This will have a significant impact."

Dye also warns that this process will be resource intensive. Also, not every product will be appropriate, so good communication between research and development and early clinical development people as to what products are actually coming through the pipeline is critical.

"Certain activities will need to be frontloaded earlier, and we will need to ensure a good supply of quality product at launch," he notes. "Some of the key considerations are where are we going to launch from – a clinical site or a commercial site?"

Because of new challenges presented by the faster approvals process and increasing emphasis on product validation is required along with a 'holistic,' lifecycle approach, says Joanne Barrick, Advisor, Global Validation, Eli Lilly & Co.

What is process validation? Barrick defines it as "the collection and evaluation of data from the product design stage through production, which establishes scientific evidence that a process is capable of consistently delivering quality products."

"A 'life cycle' approach to process validation is one that begins in development and continues through the product's life," says Barrick. "The breakthrough timeline does not mean that will be doing *less*, it means that we will be doing *more* sooner."

It also means that manufacturers will have to better understand and control input variability to assure consistent product quality and a reliable supply.

Barrick advocates focusing on the kinds of risks that may be encountered and subsequent planning as to how to mitigate a variety of manufacturing and quality risks.

"Risk assessment needs to take into account what could go wrong and the *probability* of it going wrong," she explains. "What needs to be assessed is the impact, or severity of risk, and determine what level of risk is acceptable.

Concludes on page 110.

Getting FDA Approval for Breakthrough Therapies

Continued from page 109.

Manufacturers must avoid submitting products with control strategies not sufficiently developed or robust enough to ensure that patients will be reliably supplied."

The FDA's Doleski's is first to agree. "To keep up with the demand for a breakthrough drug, manufacturers must have everything in place – equipment, production capacity and validation capacity. We don't want manufacturing issues to impede the delivery of a breakthrough product. If a breakthrough therapy does all that it promises, manufacturing delays, supply chain delays and shortages are the last thing anyone wants."

For Barrick, some of the manufacturing strategies to mitigate risk for breakthrough therapies include platform selection and using prior knowledge of similar products. In terms of equipment, manufacturers should use established models.

What are the risks inherent in early approval? Uncertainty about a product's critical quality attributes, explains Barrick, whether in materials, processing or equipment. Risk analysis is an important factor. What risk levels are acceptable and which are not?

"In the control phase we have to talk about how we can reduce risk to acceptable levels," she says. "Of course, risk assessment is a living document and we need to keep coming back to see if any new risks are introduced as a result of those controls."

FDA now has the authority with FDASIA legislation to make breakthrough therapy designations for certain drug products and recently issued draft guidance on this topic. ISPE embraces this opportunity to partner with FDA in the further development of this guidance and beyond. Going forward our goal is to collaborate with FDA on the development of risk-based CMC regulatory expectations (review and inspection) based on science and the need to deliver important medicines to the patient. ISPE's 2013 Annual Meeting, to be held 3 – 6 November in Washington, DC, will feature a session on breakthrough therapies.

Visit **http://www.ispe.org/2013annualmeeting** for more details.

She recommends some hands-on, down-to-earth, production line ways to mitigate risk, such as having multiple operators for equipment, multiple shift for operators, multiple equipment sets and process interruptions, such as personnel breaks, lunches, or weekends.

Collaboration with the FDA throughout the process is key. "Share your risks assessments, talk with the FDA," she says.

"Company senior managers should be involved at all levels to keep the process on track," Doleski advises. "Success requires intensive guidance and close cooperation between the firm and the FDA. All of the time frames are going to be compressed. Early in the process the GMP compliance states of facilities, including CMOs, must be identified."

There will have to be "creative approaches" with regard to the timing of inspections according to Doleski. There may be a two month lapse between when inspections are requested and when they are carried out. "The FDA will have to have a flexible review process," advises Doleski, "but we will still have to maintain appropriate standards for efficacy, safety and quality."

Doleski lists potential challenges. The first is having unrealistic time frames. Also, time for error needs to be factored in. There may be facility shutdowns, GMP issues, construction and manufacturing shutdowns that have to be factored in advance.

"If manufacturers are going to put time, effort and resources into a breakthrough product, it's important that we have high assurance that the companies stay compliant and that there is a high level of communication between the sponsors and the contract manufacturers about manufacturing issues that may arise," concludes Doleski. "Another potential challenge is a sponsor choosing a CMO without enough knowledge about their capabilities. How much do you know about the CMO and what type of agreement is put in place? These are important questions when you venture into an agreement with a contract manufacturer. Decisions will have to be made much earlier in the process and planning for an accelerated schedule is important."

Barrick may sum up the challenges best when she says that "the lifecycle approach to process validation provides adequate flexibility to accommodate products with breakthrough therapy designation, yet every case is likely to be unique and open discussion and sharing of risk assessment conclusions may be prudent."

As reported by Randolph Fillmore, Florida Science Communications, Inc.

ISPE Releases Data from Drug Shortage Survey

Critical report called "a deep slice of data."

Released at the *2nd Annual Conference on Redefining the "C" in CGMP*, held in Baltimore 11-13 June, data from ISPE's *Report on the Drug Shortages Survey* focused on technical manufacturing issues and their potential role in causing drug shortages. As presented by Joseph Famulare, Vice President, Global Compliance and External Collaboration of Genentech, Inc., survey highlights revealed that drug shortage causes were "multifactorial" and "multidimensional."

Famulare noted that survey responses came both from individuals (83 percent) and companies (17 percent) and, that by type, the responding companies were 62 percent manufacturers of traditional and biologic pharmaceuticals while another 7 percent were contract manufacturers. Of the companies responding, 50 percent had experienced "actual shortages," 30 percent had experienced "near misses" and 20 percent reported they had no shortages.

An ISPE Drug Shortages Project Team created the extensive survey instrument with input from global industry leaders and stakeholder groups; the survey ran in February and March 2013. The results were segmented with regard to categories of sterile versus non-sterile drugs. The data was also categorized by production issues, said Famulare, who presented "deep slices" of the extensive data the team analyzed. He noted that at some point in the analysis "the stars began to align" and themes began to emerge.

The need for companies to focus on both quality systems in production and the organization's approach to preventing shortages became apparent, said Famulare. He noted that batch issues, nonconformances, change control systems, process validation, and unspecified "other" issues in production systems were examined categorically for their potential role in shortages. For both sterile and non-sterile products, nonconformances accounted for a third of the production system issues, with the impact of process validation issues running between 20 and 21 percent.

Six manufacturing and testing systems came under scrutiny for their potential role in shortages or "near misses." They included: quality systems; material systems; production systems; laboratory control systems; facilities and equipment systems; and packaging and labeling systems. In both the sterile and non-sterile drug categories, quality systems played the biggest role in shortages and near misses, with quality systems accounting for 28.6 percent of the problems with sterile drugs and accounting for 24.7 percent of the issues with non-sterile drugs. Material issues followed with 19.5 percent of the impact for sterile drugs and 20.5 percent of the impact for non-sterile drugs.

With regard to the technical issues in the data that likely contributed to shortages, equipment problems emerged. How can these issues be mitigated? asked Famulare. "Through organizational governance, which means involving senior leadership; through process governance; and through tools and measures," he said. "The data shows that companies that have avoided shortages and near misses highly prioritize strong quality systems in manufacturing. They also link corporate goals and incentives to preventing shortages and foster relationships and communication with regulators." Famulare also noted that metrics play an important role. "Companies need to decide which metrics are important and implement them," he says.

Famulare promised that further review of the data will continue and results will be shared. ISPE will also provide a "resource toolbox" that will likely include working groups, training, publications and guidance aimed at further analyzing the data and reacting to it.

Following the report's release, Valerie Jensen, associate director of the FDA/CDER Drug Shortage Program, explained the FDA's response to the drug shortage issue. She said that "the ISPE survey aligns with what we found." Production delays and delays in capacity were largely at fault, she said. Drug shortages peaked in 2011 with 251 reported shortages. Older products were often found to be in short supply and, currently, there is a great shortage of IV nutritional drugs.

ISPE's Drug Shortage Project Team is continuing its analysis of the survey results, and Team subgroups are engaged in a series of activities aimed at addressing critical issues that underlie drug shortages. Learn more about this work at the upcoming Annual Meeting where the Team will make a presentation during Session 901-the Executive Series session on ISPE Research Initiatives. The session will be offered on Monday, 4 November from 14:00 - 17:30 in Washington, DC. In addition to strategies and innovations on drug shortages, you'll hear leading industry executives announce the results of ISPE's new research on patient experiences related to investigational medicinal products and more about ISPE's research agenda for 2014.

Concludes on page 112.

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...Drug Shortage Survey

Continued from page 111.

The FDA program on drug shortages, she said, is aimed at preventing, mitigating and resolving drug shortages. Her office updates drug shortages data daily on their website, and they encourage drug shortage reporting in order to maintain the site.

"We can only prevent drug shortages when problems are reported," she said, adding that the FDA cannot "require manufacturers to make drugs or to make more drugs." She concluded by describing a process by which the FDA could "import" drugs from foreign manufacturers to make up for shortages in the U.S., adding that "we don't want to create shortages in other countries."

The report is available online at: www.ispe.org/drugshortages/2013junereport.

ISPE 2013 Annual Meeting

Continued from page 108.

On the regulatory and quality systems front, there will be presentations on the cost of non-compliance, risk-based commissioning and qualification, new EU GMPs, and risk management during process development. The regulatory track will culminate on Wednesday with the Global Regulatory Summit, featuring regulators from the US, Europe, and Asia discussing current regulatory trends and compliance focus areas.

Two tracks will focus on manufacturing technology and manufacturing facilities. Subjects will include Facility of the Year Award, lean design in QC laboratories, single-use technology, flexible API manufacturing, PAT-based process control, aseptic processing, and other current subjects of interest to manufacturing professionals. A separate track on information systems will include clinical data and systems, use of metrics for computer system validation, and data integrity and cloud controls.

There will be three specialized focus tracks: Investigational Products Track, Project Management Track, and Young Professionals Track. Each track will run from Sunday afternoon through Wednesday morning, and each is constructed to provide a comprehensive set of subjects. Young professionals will gain a broad understanding of the many different dimensions relevant to our profession, from GMP design standards to quality and compliance. The science (and art) of project management is more than the mechanics of project scheduling and budgeting – it is about managing people. Clinical supply manufacturing will include supply chain risk management, labeling, and other specialized subjects.

Did I mention the Plenary Session? Monday morning will feature keynote presentation by the FDA's Dr. Janet Woodcock, along with Julie Kim, Global Franchise Head of Biotherapeutics, Baxter International, Inc. who will discuss "why" Baxter is expanding capacity around the globe to address plasma-derived therapies. Find out more about Julie Kim in an exclusive interview in this issue of *Pharmaceutical Engineering*.

Our industry faces new challenges, including threats from counterfeit drugs and the need to harmonize regulatory approaches. Hear the latest from regulatory authorities and industry leaders, and prepare yourself and your company to meet these and other challenges.

Lastly, ISPE's Annual Meeting wouldn't be the same without the valuable networking opportunities available throughout the week, including the exhibits and vendor interactions in addition to a variety of planned social networking events. Get to know the newer faces of ISPE or reconnect with associates and friends over a meal or cup of coffee. You won't be sorry you did!

No matter what you may be responsible for – a company, a division, a department, a process, a piece of equipment, your career – you'll find this year's Annual Meeting to be the "can't miss" event this fall for engineering, manufacturing, quality, project management and process professionals. From senior executives to the next generation of leaders, you will come away inspired for innovation and better prepared to manage risk and opportunity, every decision, every day. I look forward to seeing you there!

SEPTEMBER IS ISPE MEMBER APPRECIATION MONTH

This month, we're celebrating your contributions to your companies, your industry, to patients around the globe and of course, to ISPE.

Thank you for being an ISPE Member, and for:

Sharing best practices and stimulating information-sharing among companies and regulators to produce safe, reliable medicines that benefit patients worldwide

Organizing and participating in strong local Affiliate and Chapter networks

Volunteering your time as the world's leading subject matter experts

Your commitment to choosing ISPE as the Society of choice for your personal and professional development

Share your Member experience with ISPE and be entered to win an iPad Mini!

Visit **www.ISPE.org/MemberAppreciationMonth** for details.

ISPE has organized a month's worth of special rewards and activities:

8 – 14 September: Choose any ISPE webinar, free!

15 – 21 September: Receive brand-new content developed by select Communities of Practice.

22 – 30 September: Gain easy access to Member benefits in the brand-new Members-only resource section of the ISPE website.

Watch your email for more details, or visit www.ISPE.org/MemberAppreciationMonth

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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.

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

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

High Purity Fluid Transfer

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Integra Companies, Inc., 29 Saratoga Blvd., Devens, MA 01434. (978) 772-6166. 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.

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

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

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

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Precis Engineering, 20 South Maple St., Ste. 200, Ambler, PA 19002. (215) 540-9800. See our ad in this issue.

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Tray Systems

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

Validation Services

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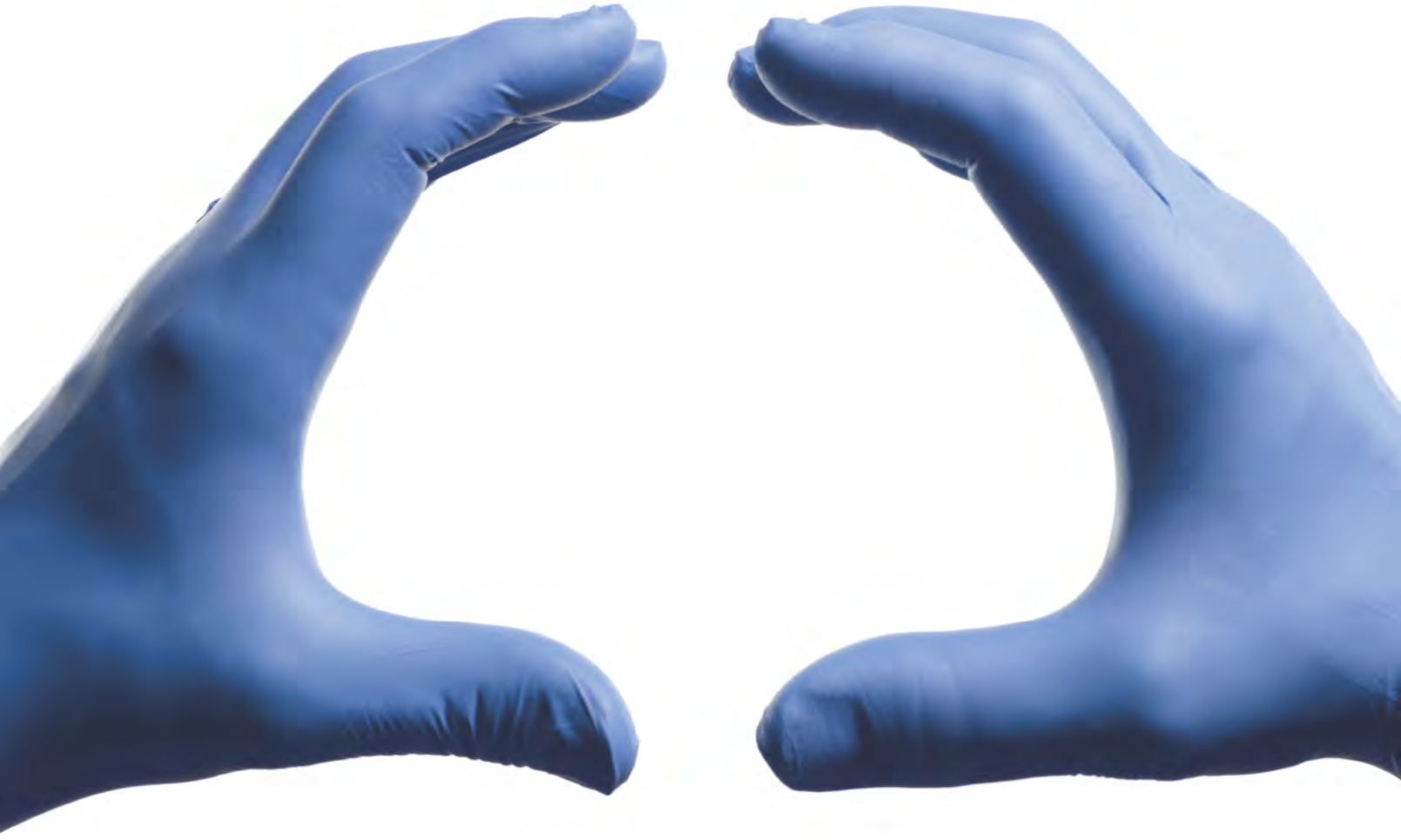

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