Science • Technology • Quality • Regulatory • Community

PDA Letter

Volume XLIV • Issue #8

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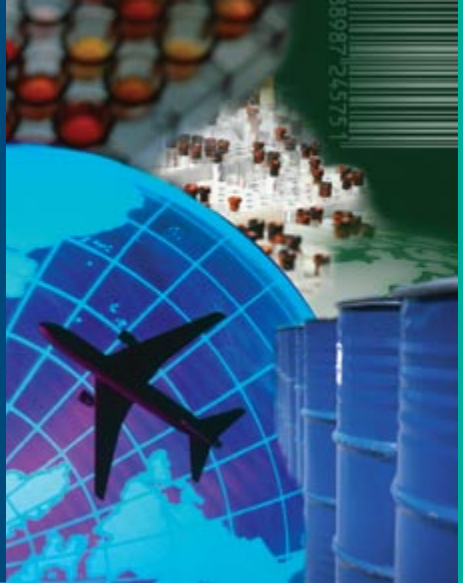
September 2008



In This Issue:

PDA
Parenteral Drug Association

Connecting People, Science and Regulation®

Dissecting the Drug Supply Chain

Management of the pharmaceutical supply change has become one of the top public health concerns with respect to consumer safety. The globalized routes of distribution for both drug components and finished products have introduced many complications that to date have yet to be solved. Unethical players and noncompliant companies along the supply chain can introduce counterfeited, adulterated and contaminated materials, often with tragic consequences. Naturally, such incidents lead to a loud and swift reaction from the public, the health authorities and the policy makers.

PDA has been on top of the issue of supply chain management throughout the year with coverage both in the *PDA Letter* (March 2008) and the *International Pharmaceutical Quality* (May/June 2008). Partnering with the U.S. FDA, the Association has organized a meeting on the topic this September.

The *PDA Letter* continues this effort with a compilation of perspectives from four experts this month. Management of incoming raw materials and components is the subject of articles by **Stein Lokstad,** General Manager, Brenntag, and **Mads Reedtz Espersen,** Principal Scientist, Novo Nordisk. Strategies for managing the distribution of temperature-sensitive drug products are the focus in articles by **Rico Schulze,** GMP Inspector, Dresden Inspectorate, and **Nina Heinz**, Quality and Solutions Manager, LifeConEx.

Lokstad's article, "Combating Weaknesses in the Pharmaceutical Supply Chain" (p. 26), highlights ingredient producers and distributors' part in the supply chain process and reviews available tools for securing supplies. Espersen provides a case study which outlines how Novo Nordisk ensures the highest quality from its container closure vendors in his article, "Supplier Relation Management within Quality – Aiming to be the Preferred Customer" (p. 20). Schulze provides a commentary on the importance of good cold chain management practices from the warehouses and shipping docks at the pharmaceutical company all the way through to retail outlets and hospitals/clinics. His commentary, "A Chance for Harmonization?," begins on page 24. Finally, Heinz's article, "Solution to End-to-End Temperature Controlled Transportation: Uniform Labeling?" (p. 16), addresses the challenges in developing standardized labeling for temperature-sensitive shipments.

2009 PDA Annual Meeting

The Impact of the Microchip – Application of Modern Technologies in the Development, Manufacture and Testing of Bio/pharmaceutical Products

April 20-24, 2009

Las Vegas, Nevada

Conference	April 20-22, 2009
Exhibition	April 20-21, 2009
Career Fair	April 20-21, 2009
Courses	April 23-24, 2009

red rock
CASINO · RESORT · SPA
Las Vegas

Join industry and regulatory colleagues at the *2009 PDA Annual Meeting* to explore some of the most influential factors impacting the current state and future development of the pharmaceutical and biopharmaceutical industry. Built on the theme, *The Impact of the Microchip – Application of Modern Technologies in the Development, Manufacture and Testing of Bio/pharmaceutical Products*, the conference will examine the systems and tools that can help you and your company maximize efficiency and productivity, while consistently delivering safe, pure and reliable drugs to patients.

Complementing the conference are PDA Training and Research Institute (PDA TRI) courses, an exhibition featuring today's leading bio/pharmaceutical companies and service providers, PDA's 5th Annual Career Fair and enhanced networking opportunities that take advantage of all that Las Vegas and the exciting Red Rock Resort and Casino have to offer.

Increase your knowledge, find solutions to every day challenges, make valuable contacts and advance your career at the *2009 PDA Annual Meeting*.

Photos courtesy of Bayer Healthcare and Sartorius Stedim Biotech

www.pda.org/annual2009

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Cover art:
The safety and quality of materials traded in the global pharmaceutical supply and distribution chain have become a top concern in recent years.

Coming Next Issue:
Reports from the PDA/FDA Joint Regulatory Conference

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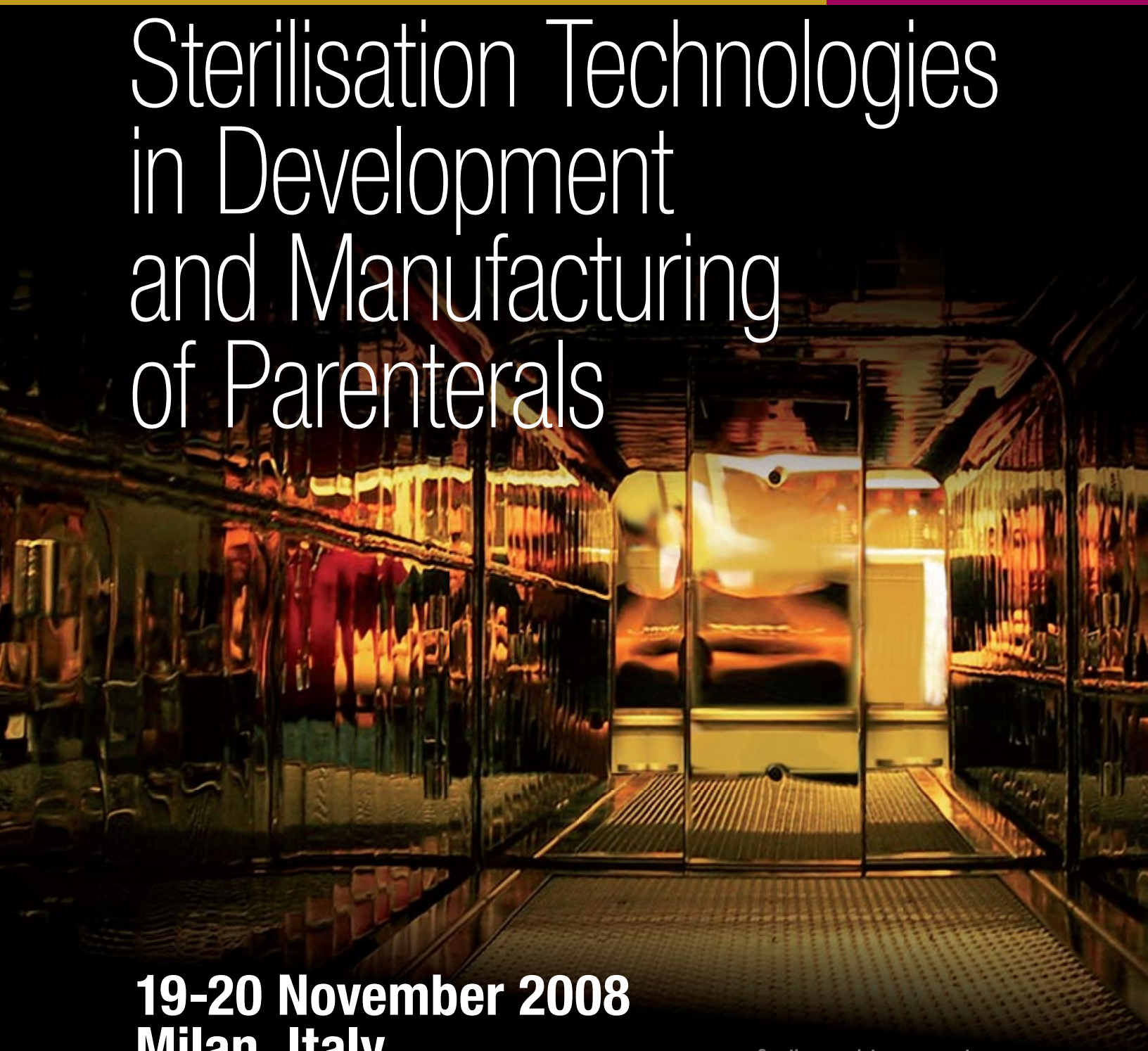
Sterilisation Technologies in Development and Manufacturing of Parenterals



19-20 November 2008
Milan, Italy

See the complete program at:
www.pda.org/europe

Conference, Exhibition: 19-20 November
Workshop: 18 November
Training Course: 17-18 November

This conference will give an overview and a technology update of the most relevant sterilisation techniques used in the pharmaceutical and in the medical device industry. The sessions will address technology and microbiology issues and regulatory aspects. Experts from industry and regulatory authorities will present practical information illustrated by case studies.

Register by 17 Oct 2008 and SAVE!

Editor's Message

Making Safe Product

As explained on the cover of this issue, the quality of supplies sourced from overseas has risen to one of the top public health concerns with respect to consumer safety. PDA members—whether representing regulators, manufacturers, suppliers, consultants or academia—work hard every day to ensure that patient's receive the safest and most effective drug products available.

While PDA members can get caught up in the details of specific issues like risk management, validation, analytical methods and quality by design, they shouldn't lose sight of the fact that all of these discussions pertain to the overall quality, safety and effectiveness of the very important drug products consumed by patients worldwide.

In this issue, four members share their perspectives and experiences on the management of the pharmaceutical supply chain. There is no need to recount what can happen when the supply chain breaks.

Another important consideration in manufacturing a drug product is the safety of materials that the product comes into contact with during processing, storage and dispensing. The PDA Disposables Task Force is taking on the issue of the safety of single-use equipment; an update on the group's activities so far is included in the Science & Technology Snapshot in the "Task Force Corner."

The Product Quality Research Institute's Parenteral and Ophthalmic Drug Products (PODP) Working Group is also concerned with the impact on drug safety from extractables and leachables. PDA is strongly supporting the group's effort, and hosted their first meeting in June. A "PQRI Update" in the Science & Technology Snapshot details the PODP Working Group's progress.

PDA Letter

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WHO, PDA Enter Formal Cooperative Training Arrangement

PRESIDENT'S MESSAGE

Bob Myers

I am pleased to announce PDA's latest collaboration, a cooperative agreement with the World Health Organization (WHO) to advance knowledge and standards regarding pharmaceutical cold chain management.

I wrote a few months ago about the power of collaboration, and in recent year's PDA and its members have worked extremely hard to expand our network of partners as part of our ongoing efforts to *Connect People, Science and Regulation®.* This latest agreement with WHO epitomizes these efforts.

Our ongoing work with WHO began in 2006 at the PDA Cold Chain Conference in Berlin. Since then PDA's Europe Office, the PDA Pharmaceutical Cold Chain Interest Group (PCCIG) and the WHO's Department of Immunization, Vaccines and Biologicals (IVB), Quality and Safety Standards sponsored a training course for pharmaceutical professionals to better understand the entire scope of the "cold chain." The first offering of the course took place in Turkey this past June. WHO's **Umit Kartoglu,** PhD, provided an overview of the unique training "on wheels" at the *2008 PDA Biennial Training Conference* last May. PDA PCCIG leader **Rafik Bishara,** PhD, helped develop and teach the course with Dr. Kartolglu.

The agreement recently reached with WHO ensures that the two organizations will continue to work together and harmonize efforts to disseminate information regarding pharmaceutical cold chain management, technology and training.

Other PDA collaborations continue to progress. Recently, PDA and the EMEA reached an agreement to hold our third Joint Conference. Details of this event are included in the related story on the next page. In addition, PDA and representatives of China's Shanghai Municipal Food and Drug Administration continued discussions in July on future collaborations following our successful Quality Systems workshops last May. In November, PDA is teaming with ISPE and PIC/S to sponsor a workshop on Annex 1.

And of course, PDA is extending our longest and most fruitful continual collaboration with the U.S. FDA at our annual PDA/FDA Joint Regulatory Conference. This meeting has grown significantly in stature and quality since its inception, and we anticipate this year's event to continue that trend.

This year, PDA worked with FDA to develop an agenda for a two-day meeting on pharmaceutical ingredient supply chain, which we appended to the end of the regular PDA/FDA conference. Our goal is to offer this timely meeting again at locations convenient to our members and industry stakeholders across the globe.

With that, I'd like to thank all of our collaborative partners for working with us, and I look forward to our future joint efforts.

PDA, EMEA Agree to Third Joint Conference

The number three is an important milestone for many things. In life, three times is generally the charm. In baseball, three strikes are all you get before you are out. Many believe that good fortune or misfortune happens in three. And in pharmaceutical manufacturing, it takes three lots to validate.

When it comes to the PDA/EMEA Joint Conference, the third event is significant for many reasons: One: it confirms that the first two—London in 2006 and Budapest in 2008—were undeniable successes. The quality of the content of each meeting attracted large numbers of industry and regulatory representatives who met to discuss the most pressing topics at the time. Two: it signifies that this is one of PDA's top "signature" events along with the Annual Meeting and the PDA/FDA Joint Regualtory Conference. Three: it validates PDA's belief that the Association through the hard work of it members is *Connecting People, Science and Regulation*®.

The committee developing the *2009 PDA/EMEA Joint Conference* is working with PDA's staff in Europe to find the perfect location for the event. Tentatively, the event could take place in either Berlin or Amsterdam; the *PDA Letter* and *PDA Connector* will provide updates on the venue as they are available. Target dates for the event are:

October 13–14, 2009 for the **Conference**

October 13–14, 2009 for the **Exhibition**

October 15–16, 2009 for the **TRI Training**

Keep an eye on the "News and Notes" section for more updates on this exciting PDA event.

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2008 PDA

Pharmaceutical Cold Chain Management

Current Good Distribution Practices

4-5 November, Berlin, Germany

Conference/Exhibition: 4-5 November
Training Course: 6-7 November

See the complete program at:
www.pda.org/europe

- Container, Packaging Development, Simulation, New Concepts
- Controlled Shipping
- Regulatory Session
- Validation/Qualification of Distribution Channel
- Technology used in the Supply Chain
- Cold Chain Case Studies

Science & Technology *Snapshot*

PDA Seeks Editor for Journal

Rich Levy, PhD, PDA

Lee Kirsch, PhD, Editor of the PDA Journal of Pharmaceutical Science and Technology, has decided to step down from his position.

Lee's departure leaves us with a feeling of loss, as well happiness for his opportunity to move on to other challenges. His eight-year tenure with PDA was marked by editorial consistency, a broadening of content and page count, and ever increasing quality of the review, editing and publication process. The future for the PDA Journal is brighter for Lee's contributions and hard work.

Upon resigning, Lee said, "I have very much enjoyed my eight-year tenure, and I have appreciated the opportunity to work with the PDA staff and leadership, the Journal Editorial Board and all of our authors. The PDA staff and Editorial Board have been consistently supportive and professional in responding to the needs of the Journal and in considering my advice and opinions. I believe that the Journal is much improved and vibrant as a result of our joint efforts."

Effective immediately, I will assume the position of Acting Editor until we complete the search for a new Editor. **Walter Morris,** Director of Publications, will help me in fulfilling this new role as necessary and in reviewing of candidates for the Editorial position.

Salil Desai has graciously agreed to continue on in his current role as Assistant Editor and to assume some of the activities Lee was handling until he has finished his PhD program later this year.

That being said, we now need to move forward with the process of hiring a new Editor. I would like to invite each PDA member to recommend qualified candidates. That could include throwing your own hat into the ring!

Please respond directly to me at pdajournaleditor@pda.org; I would be happy to consider your input or application.

Technical Report *Watch*

In Global Review: *Drafts of the following TRs are under review by the global PDA membership. To comment on any one of the drafts, go to* https://store.pda.org/review/login.aspx

- ***Points to Consider: Microbial Data Deviations***

In Edit: *After global review, task forces responsible for the TRs consider the feedback received. TRs then undergo final technical editing.*

- **TR-22 (Revised),** ***Process Simulation Testing for Aseptically Filled Products***
- ***Biological Indicators for Sporicidal Gassing Processes: Specification, Manufacture, Control and Use***

In Board Review: *Following technical editing, TRs are reviewed by PDA's advisory boards (SAB, BioAB). If/when approved, the PDA Board of Directors (BoD) makes the final decision to publish or not publish the document as an official PDA TR. Balloting at each level can take several weeks or longer, depending on the questions posed or revisions required.*

- ***Blow-Fill Seal*** **(BoD)**
- **TR-15 (Revised),** ***Validation of Tangential Flow Filtration in a Biopharmaceutical Application*** **(BioAB)**

In Publication: *TR is approved and ready for publication with next Journal*

- **TR-14 (Revised),** ***Validation of Column-Based Separation Processes*** **(July/August Journal)**
- **TR-26 (Revised),** ***Sterilizing Filtration of Liquids*** **(September/October Journal)**
- **TR-41,** ***Virus Filtration*** **(September/October Journal)**

Journal *Programs*

Predoctoral Fellowship Grants Awarded

PDA and the Journal of Pharmaceutical Science and Technology is pleased to announce the recipients of its third annual Predoctoral Fellowships. The recipients each will receive a $10k grant from PDA to help them conclude their doctoral research. PDA congratulates each winner, their sponsoring professor and the institutions at which they attend.

Each winner is listed below along with the name of their research, their sponsoring professor and their university.

Sajal Patel for "Characterization of Heat and Mass Transfer for Freeze-drying in Syringes"; Michael Pikal, PhD, University of Connecticut

Bhargavi Knodragunta for "Quality by Design using High-throughput Bioreactors with Feedback Control to Predict Multivariable Relationships"; Antonio Moreira, PhD, University of Maryland

Vinayagam Kannan for "Optimization of formulation and process parameters in the development of parenteral echogenic liposomes containing paclitaxel for ultrasound mediated, targeted drug delivery to solid tumors"; George Wood, PhD, University of Tennessee

Sok Bee Lim for "Parenteral delivery of TREM 1 peptide (LP17) using sterically stabilized phospholipid micelles for the treatment of rheumatoid arthritis"; Hayat Önyüksel, PhD, University of Illinois

Task Force *Corner*

Single-Use Tools: A Focus of the Disposables Task Force

Emily Hough, PDA

Rob Repetto, Director Manufacturing Sciences & Technology, Wyeth, the Disposables Task Force leader, has unveiled some of the Task Force's recent and upcoming plans to the *PDA Letter.*

Repetto has shared that the Disposables Task Force will be discussing how to roll out a training program for single-use systems at PDA's Training Research Institute. This will build on the success of the two-day training workshop that was held after the *2008 PDA/EBE Conference on Biopharmaceutical Development and Manufacturing* which was sponsored in conjunction with PDA and Sartorius Stedim Biotech. The workshop covered many aspects of single-use systems such as, filtration, bioreactors, connectors and applications.

After the same meeting on June 26, members of the Disposables Task Force met to discuss methods of disposing of single-use systems: incinerations, recycling and co-generation being a few of the most common options. Manufacturability issues related to how and why single-use systems are used in the process were also raised. According to Repetto, often the answers depend on where you are using the component and how close the material being

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Journal *Preview*

Japanese Perspective on Aseptic Processing

The July/August edition of the *PDA Journal of Pharmaceutical Science and Research* features two papers by a team of researchers, including a member of Japan's health authority. Both papers examine different aspects of aseptic processing.

The following is the full list of July/August article:
"Proposal for a New Categorization of Aseptic Processing Facilities Based on Risk Assessment Scores"; by Hirohito Katayama, Atsushi Toda, Yuji Tokunaga and Shigeo Katoh

"Monitoring Minimization of Grade B Environments Based on Risk Assessment Using Three-Dimensional Airflow Measurements and Computer Simulation"; Hirohito Katayama, Takashi Higo, Yuli Tokunaga, Shigeo Katoh, Yukio Hiyama and Kaoru Morkiawa

"In Vitro Permeation of Carvedilol through Porcine Skin: Effect of Vehicles and Penetration Enhancers"; Y. Madhusudan Rao, Ramesh Gannu, Y. Vamshi Vishnu and V. Kishan

continued on page 13

PQRI *Update*

Parenteral and Ophthalmic Drug Products (PODP) Leachables and Extractables Working Group

On June 24, 2008, The Product Quality Research Institute's (PQRI) as Parenteral and Ophthalmic Drug Products (PODP) Working Group (a follow-on to the PQRI Leachables and Extractables Working Group) met at PDA's headquarters to initiate the process for development of Thresholds and Best Practices for the following drug product categories:

- Large Volume Parenterals (LVP)
- Small Volume Parenterals (SVP)
- Prefilled Syringes and Ophthalmics

The toxicology subteam planned to investigate the application of Safety Concern Threshold (SCT) and Qualification Threshold QT) for each category. A proposed Thresholds model is planned for October 2008.

continued on page 12

PQRI Update, PODP Leachables and Extractables Working Group Progress Update, continued from page 11

The chemistry subteam planned to investigate the possibilities for acquiring a unique six component container closure system in which the individual components would be profiled as well as conducting a leachable study on the assembled system. The system would be representative of the base resin materials, adhesives, overwrap and labels. The materials would be consistent with a combination of those used in each of the four categories and would serve as a model to acquire data to demonstrate a controlled extraction study followed by a leachable study. In addition, the potential post-filled processing conditions, such as terminal sterilization and priming of materials of construction, such as irradiation, will be considered to determine the effect on the leachable profile for the proposed six component container closure system.

There are six different solvents currently being considered for the study with special attention given to aqueous systems. Headspace sampling and inorganic methodology are also being conceived. Commitments from material suppliers and processors for radiation services are being pursued followed by assignments of laboratory resources. The supplier commitments, plan and draft protocols for Best Practices, are scheduled to be completed by October 2008. The next face-to-face meeting will be held in the fourth quarter of this year.

The PODP Working Group evolved out of the work of the PQRI Leachables and Extractables (L&E) Working Group. In 2006, L&E proposed and submitted to the U.S. FDA the recommendation document, *Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products (OINDP),* which introduced the concept of safety and qualification thresholds for organic leachables in OINDP and illustrated the principles of conducting controlled extraction studies with correlation to leachables.

Along with submitting the recommendation document to FDA, several national and international workshops were held to convey the value of using this approach. The workshops were well attended and well received by industry and FDA. The regulatory concern for interaction of inhalation products with package components is at the highest level of concern and this model for developing thresholds using best practices is now an accepted standard for OINDP.

There are other dosage forms that have a high concern level for likelihood of drug product-package interaction; however, the established safety threshold can only be applied to OINDP. Great interest in how the threshold concepts can be applied to other dosage forms such as parenteral and ophthalmic drug products swelled to the surface. The packaging components, dosing, duration and products are diverse for these products which makes the application of the safety threshold complex due to the combination and use of the various products.

In the spring of 2007, a proposal was made to PQRI by the members of the Leachables and Extractables Working Group stating that the "good science" best demonstrated practices established for the OINDP pharmaceutical development process can be extrapolated to container closure systems for PODP. The proposal was accepted and subsequently a work plan was approved in the spring of 2008, which led to the formation of the PODP Working Group. The schedule for the work plan is available at www.PQRI.org.

Journal Preview, Predoctoral Fellowship Grants Awarded, continued from page 11

"Selective Drug Delivery to the Colon Using Pectin-coated Pellets"; Du Qing, He Wei, Cao De-Ying, Fan Li-Fang and Xiang Bai

"High-Pressure Treatment, a Potential Antimicrobial Treatment for Pharmaceutical Preparations? A Survey"; Hans van Doorne

"In Vitro Evaluation of Porous Carrier-based Floating Granular Delivery System of Orlistat"; Sunil K. Jain, G. P. Agrawal and N. K. Jain

"Preformulative Assessment of Preformed Complexes of Gemfibribrozil with Cyclodextrins"; Kamla Pathak, Shabnam Ain and Betty Philip

This issue also includes the table of contents from the *The Thai Journal of Pharmaceutical Science* as part of the "Journal Alliance" formed between the two journals.

Task Force Corner, Single-Use Tools, continued from page 11

processed is to the final product. **Jerry Martin,** Sr. VP, Scientific Affairs, Pall Corporation, **Morten Munk,** VP, CMC Biopharmaceuticals and Repetto were present.

Currently the Task Force has established an extensive list of topics related to single-use equipment for manufacturing and formed several subteams to develop a document draft of best practices. The Team felt that the Task Force and technical document they have developed should be renamed to "Single-Use Systems" rather than "Disposables" to better reflect the full range of manufacturing systems which have become single-use.

The latest meeting for the Task Force took place on July 25; the purpose of that meeting was to establish the subteams and subteam leaders for the various sections to be included in a final technical report. A full task force teleconference is planned for August 13 and a face-to-face meeting is scheduled for September 11 after the *2008 PDA/FDA Joint Regulatory Meeting.*

The Disposables Task Force is interested in members who have a background with the EPA and biohazard waste disposal. For more information about the Task Force, email Robert Repetto at Repettr@wyeth.com.

Pharmaceutical and Biopharmaceutical Career Opportunities Abound...

www.pda.org/careers

PDA Career Center

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Whether you are actively seeking employment, or just want to see what you might be missing, PDA's Career Center delivers a wide range of opportunities. Post as much or as little information as you like. Our 100% confidential and secure job-searching network allows you flexibility and ease-of-use without the risk.

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PDA℠
Parenteral Drug Association

PDA Interest Groups & Leaders

PDA Interest Groups are divided into five sections by subject matter. This aligns them for improved effectiveness, supports increased synergies and provides the opportunity for Interest Group members to play a more active role in Task Forces. The five sections are Quality Systems and Regulatory Affairs, Laboratory and Microbiological Sciences, Pharmaceutical Development, Biotechnological Sciences and Manufacturing Sciences. PDA's goal is for each group to have co-leaders from the three major regions in which the Association is active: Asia, Europe and North America. Any PDA member can join one or more Interest Group by updating their member profile (www.pda.org/volunteer). Please go to www.pda.org/interestgroups for more information.

SECTION TITLE

Biopharmaceutical Sciences	Laboratory and Microbiological Sciences	Manufacturing Sciences	Pharmaceutical Development	Quality Systems and Regulatory Affairs

SECTION LEADER

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Solution to End-to-End Temperature Controlled Transportation: Uniform Labeling?

Nina Heinz, LifeConEx

In striving to ensure that their products arrive at destination at the right time and in the right condition, many pharmaceutical companies have developed labels to indicate how their shipments are to be correctly handled during transportation. Forwarders, airlines, ground handling companies and other involved parties along the transportation chain are now facing the challenge of an increasing number of these labels.

Lack of consensus among the parties involved regarding the images and wording to be used on labels has become problematic. These labels aim to get across similar messages indicating the sensitive nature of the product but use different wording and images to convey the adequate instructions. Although well intentioned, there is no industry-wide standard label and the multiple variations of labels often cause confusion.

The International Air Transport Association (IATA) Perishable Cargo Regulations (PCR) chapter on package labeling addresses the need for an industry standard: "A label or marking on the containers would provide the best, safest and surest means of communicating the time/temperature sensitivity of freight from the health care industry. Although not mandatory, it is recommended that such a label would help to expedite the movement of the cargo and avoid inadvertent and improper storage of passive packages and active systems."

It is in the interest of all parties involved to agree on a standard label to be used worldwide and binding to all IATA airline members, providing clear handling instructions to ensure the safe transportation of the shipments under the required temperature conditions. The message on the label should be very simple and easy to understand, with clear instructions on the temperature conditions required during transportation and storage. As English is the official IATA language, this should also be the language used for such labels.

In chapter 17 of the IATA PCR examples of labels indicating "Time and Temperature Sensitive" products are proposed. The labels use clear symbols that are simple and should be understood on a global level. Although these labels communicate the time and temperature sensitive nature of the goods, they do not provide clear instructions on what actions are to be taken based on this information. The labels need to primarily indicate not only that the shipment is temperature sensitive but at what temperature this package should be maintained throughout the transportation chain.

Although a general consensus exists identifying labeling as a very important issue, it is also a heavily debated topic with a wide range of opinions and concerns. For example, identification of the commodity type and the temperature are two critical elements that could be placed on the shipping label. Below I outline the pro and con positions for both.

1. **Should the label identify the shipment as a pharmaceutical product?**

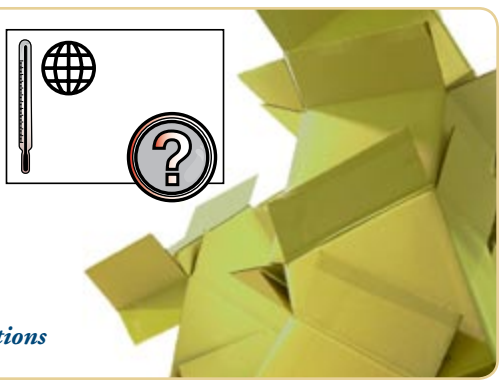
   Pro: Identifying the shipment as pharmaceutical shipment would ensure that these goods are handled by all parties involved with special care. The general awareness would be raised so those handling the shipment would be alerted to the critical nature of these goods and the need to provide correct (additional) services such as special storage.

   Many pharmaceutical companies also strive to ensure that their pharmaceutical products are stored separately from other perishable products such as flowers, fruit and fish. The segregation of products is a key aspect to maintaining the integrity of pharmaceutical products. In practice, this is very difficult for many airlines and ground handling companies to implement due to the restricted storage capacity available at the required temperature. Most airlines adhere to the IATA principles of co-loadability based on commodity type, thus pointing out that whatever can be loaded side by side in an aircraft as per IATA regulations, can also be stored side by side in a warehouse. The packaging plays an important role in protecting the pharmaceutical product from any such outside influence and should be designed to ensure that product integrity is maintained.

   Con: Some pharmaceutical companies are weary of using labeling for fear of drawing unwanted attention to their high-value products with a risk of theft or pilferage. It can be of course argued, that the risks of mishandling due to lack of clear instructions are even greater, however the concern that such a ➤

"A label or marking on the containers would provide the best, safest and surest means of communicating the time/temperature sensitivity of freight from the health care industry."

— IATA Perishable Cargo Regulations



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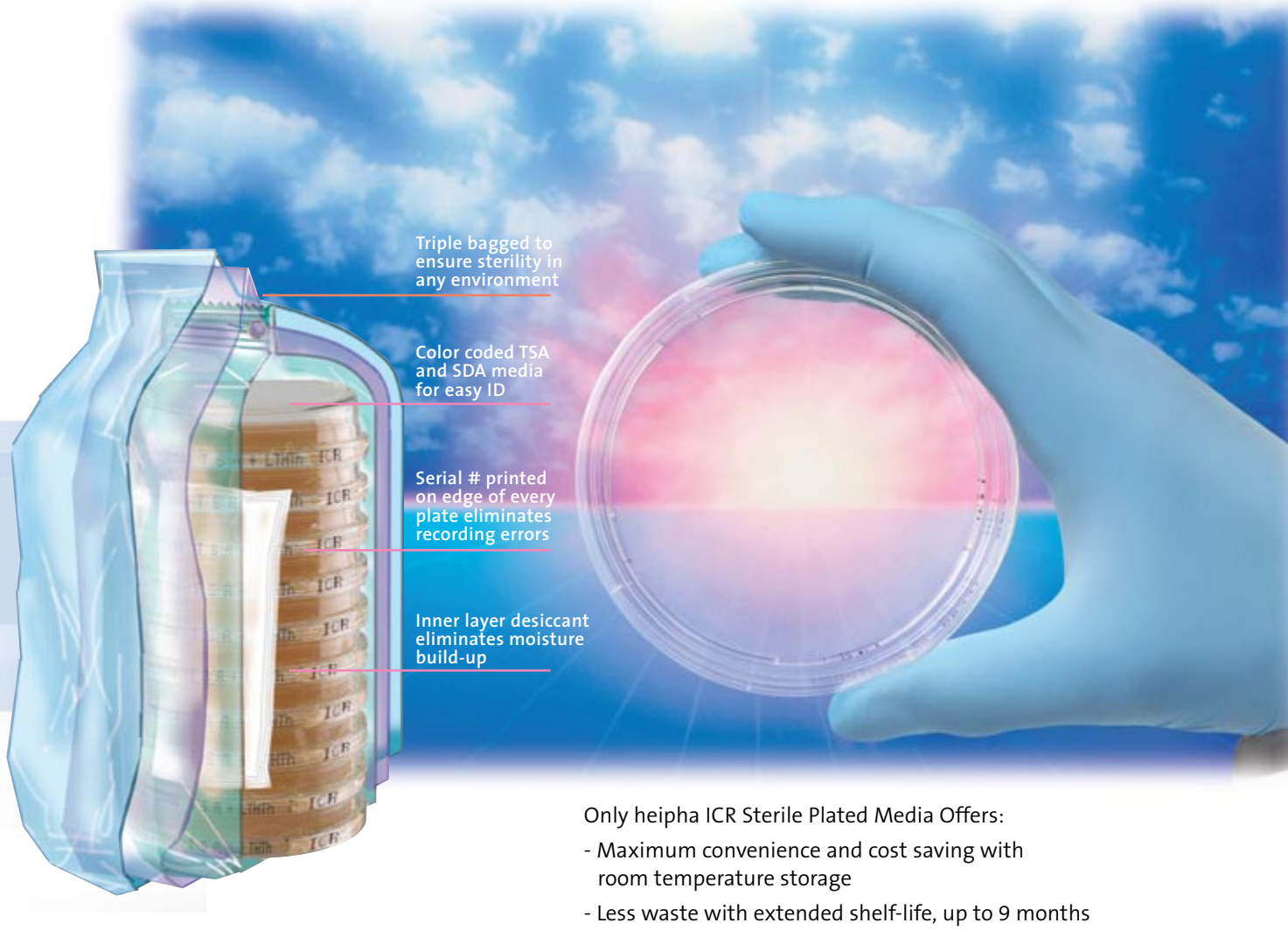

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label identifies the shipment as a high-value and thus theft endangered shipment is very serious.

This risk could be minimized by having a general perishables label proving only storage and handling instructions and not referring in any way to the shipment contents.

2. **Should the label indicate a temperature range?**

Pro: Providing clear handling temperature requirements on the label is welcomed by many as this would provide direct instructions to the staff handling these shipments on an operational level in the warehouse, on the tarmac, etc. Although the implementation of standard operating procedures (SOPs) remains a critical and very important part in ensuring the transportation of pharmaceutical products, instructions need to be provided not only at the office level but also at the operational level. Labels using little wording but providing clear instructions with numbers and images will provide guidance to the involved staff.

Con: Many airlines are weary of the implications of any temperature specifications on the label with regards to the possible liability that this implies for the carrier. Storage capabilities and handling conditions vary from one station to the next, thus most airlines are unable to offer the required conditions on their worldwide network. Temperature controlled storage capacities at airports are limited, and airlines store the pharmaceutical products at the required conditions wherever possible. An assessment and a mapping of station capabilities need to be made ahead of time together with the carrier when setting up the SOPs.

In addition, temperature control in-flight remains very limited and very few studies have been made to provide detailed information on the possibilities as well as the reliability of such heating/cooling systems in the different aircraft types.

Many parties also argue that any temperature indication will only cause additional confusion. The temperature data related to a single shipment can be very complex including aspects such as:

- Difference between the product temperature and the temperature at which the shipment should be transported. For example, a +2–8°C product may be packaged in such a way that the ideal temperature during transportation should be at +15–25°C. The label must indicate the temperature at which the package should be transported and stored, keeping in mind that this is not necessarily the same as the product temperature.

Many airlines are weary of the implications of any temperature specifications on the label with regards to the possible liability that this implies for the carrier

- Difference in the temperature requirements during transportation and the storage conditions needed at origin. Storage instructions for the consignee upon retrieval of the goods (for example: open immediately and store at +2–8°C) do not apply to the transportation under the responsibility of the airlines. Critical situations may occur when shipments need to be kept at a different storage conditions upon arrival at destination. For example, a shipment may need to be transported at +15–25°C from origin to destination airport, but should then be stored at the airport warehouse at +2–8°C while waiting for customs clearance and retrieval by the consignee.
- Certain shipments are also shipped in packaging validation for a certain number of hours. In the case of a delay where this time period is greater, intervention is necessary to handle the shipment according to predefined measures in the SOP. For example, a shipment may have to be transported at +15–25°C but in case of delays causing the total transport time to be greater than 96 hours, the shipment should be moved to a +2–8°C cool room.

Taking this a step further, an approach similar to the IATA Dangerous Goods regulations should be considered for the future. Such measures would ensure not only standardized labeling based on product groups, but also mandatory handling procedures, storage requirements and trainings. Parties would be certified by IATA for the transportation of temperature sensitive life sciences shipments in airfreight based on a recognized worldwide standard.

Proper handling and storage along the entire chain needs to be evaluated on an individual basis, taking into consideration the packaging, routing, airport handling, warehouse conditions, customs clearance and many other important factors. If the capabilities and infrastructures of airlines, groundhandlers and airports are not clearly pre-examined and mapped, labeling will provide additional awareness but will not be sufficient. Emergency situations such as an extended customs clearance or flight delay due to bad weather conditions will always require the close monitoring of all shipments and intervention based on agreed upon SOPs and trained staff. In urgent

situations where the time frame of the packaging validation is passed the limit and the shipment needs to be stored in a cool room, the knowledge of available facilities, a clear understanding of the packaging handling requirements and predefined communication measures are vital in safeguarding a shipment.

Uniform labeling meeting the requirements of both the pharmaceutical industry as well as the air freight industry will pave the way to ensure that shipments are identified with clear instructions. Labels do not in any way however, replace the need to implement clear SOPs as approved and understood by all parties involved and closely monitored to ensure compliance for every shipment.

About the Author

Nina Heinz is the Quality and Solutions Manager for LifeConEx (www.lifeconex.com), the only industry-specific provider of integrated end-to-end temperature controlled transportation solutions for the life sciences industry. LifeConEx is a joint venture between DHL Global Forwarding and Lufthansa Cargo. Prior to her involvement with LifeConEx, Nina was with Lufthansa Cargo for several years as a global account manager for key pharmaceutical customers in Europe. She played a key role in the development of the Cool/td service offer, designed and implemented to meet the requirements of the pharmaceutical industry for the transportation of temperature sensitive products in airfreight. Nina was one of the founding members of the Pharma Logistics Forum (also known as the PLF) and was closely involved in the coordination of the annual conferences as well as an active member of the ongoing working groups with key players of the industry.

Supplier Relation Management within Quality – Aiming to be the Preferred Customer

A Case Study on Managing Product Packaging Supplies

Mads Reedtz Espersen, Novo Nordisk

The pharmaceutical industry is facing increasing quality requirements and expectations for drug products and subsidiary container closure systems from both health authorities and patients. In response to these demands, the industry is obliged to approach the supplier cooperation differently than what applies for commodities.

Based on risk assessment, the quality of primary packaging materials can be considered as critical factors for the overall drug product. As a pharmaceutical company, Novo Nordisk considers the quality of our products, services and the way we work to be essential competitive parameters of our business. In order to provide quality products to our customers (i.e., the patients), we are obliged to work with the suppliers that have the strongest commitment to quality.

Assessment

Potential new suppliers of primary packaging materials are vetted thoroughly prior to approval. Already approved suppliers are routinely assessed, benchmarked and challenged to continuously to improve quality of their products and services.

Assessment of potential new suppliers includes on-site auditing of the quality management system (QMS) and an evaluation of the company's social and environmental responsibility. In addition, examination of the production capacity as well as commercial and financial aspects is conducted in the overall assessment.

Furthermore, primary packaging materials, manufactured according to Novo Nordisk specifications, are tested on at least three consecutive test batches before approval. The tests comprise QC testing according to quality specifications, drug compatibility tests (as applicable) and comprehensive machine ability tests in all relevant pharmaceutical manufacturing processes.

Approved supplier's QMS are typically audited biennially; however, the audit frequency may vary based on supplier performance. Novo Nordisk performs an annual quality evaluation and relative benchmarking on product quality, quality system performance, timeliness and innovation for each approved supplier of primary packaging materials.

A data warehouse based quality surveillance system is under construction. This system will be used to compile data from QC tests on delivered batches for the annual reporting, trending and benchmarking of quality performance.

Specifications:

Specifications for primary packaging are based on several inputs, including:

- Regulatory requirements
- Container closure system design and interface requirements
- Risk assessment
- Customer requirements
- Internal manufacturing process requirements

For primary packaging materials, the following specification package is established:

- Item specification
- Drawing
- Delivery specification
- Quality specification
- Measurement methods (including estimated, expanded measurement uncertainty)
- Image limiting reference archives (pictorial definitions of cosmetic defects)
- Quality system agreement
- Definitions
- Inherited cGMP requirements to line clearance, change control, hygiene, training, traceability, sampling, warning procedure, preventive maintenance, calibration, handling of measurement uncertainty, re-processing

References and Standards

Industrial standards are applied to the greatest extent possible to enhance harmonization and feasibility in relation to suppliers.

The prevailing standard for quality management systems is the ISO 9001:2000, even though the fairly new ISO 15378:2006 is gradually becoming an industry standard. ISO 15378:2006 combines the ISO 9001:2000 requirements with the applicable cGMP requirements for manufacturers of primary packaging materials.

Statistically based QC sample testing (AQL-testing) is based on ISO 2859-1:1999 for testing by attributes, and ISO 3951-1:2005 and ISO 3951-2:2006 for testing by variables.

ISO 14253-1:1998 is used for the handling of measurement uncertainty at supplier and customer; the customer in this case being the pharmaceutical company. According to the standard, the supplier proves conformance to specifications by deducting estimated expanded measurement uncertainty from the tolerance zone. In contrast, the customer proves non-conformity by adding the estimated expanded measurement uncertainty to the tolerance zone.

Beyond Compliance

Quality is commonly defined as meeting or exceeding expectations and needs of the customer and society, thus meaning that quality is more than merely compliance. ➤

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No matter how extensive the "specification web" is, it will not assure "zero defect" quality because:

- Defining all possible types of defects is not feasible
- Testing for numerous types of defects becomes excessively resource demanding
- Testing based on samples and statistics will always be associated with a certain finite confidence level
- Some defect types may be embedded and hence not visible on the packaging material, revealing themselves later in the lifecycle

"Quality Mindset"

The highest achievable level of quality cannot be based solely on specification testing and auditing. This commitment to quality must be built into the product design as well as the manufacturing and handling processes.

At Novo Nordisk, we strive for this highest level of quality by applying the "Quality Mindset." "Quality Mindset" is about being beyond compliance, assuming responsibility, being innovative and cooperative while continuously learning from both mistakes and successes.

In actual practice, we apply the "Quality Mindset" with respect to our suppliers by aiming to:

1. Make expectations clear prospectively, i.e., establish unambiguous and appropriate specifications and maintain written and consented agreements. Validate the supplier's measurement and verification methods (intercalibration) at an early stage of the collaboration. We find it important to narrow any gap between the suppliers and our expectations to the absolute minimum to avoid misunderstandings.
2. Share knowledge by striving for a profound knowledge of each others' processes. This mutual understanding of processes allows us to focus on the "customer's customer," i.e., the patient. The more mutual knowledge, the better the communication and understanding can be.
3. Learn from mistakes by maintaining a painstaking persistence in finding and disclosing root causes for discrepancies. Implement and verify the effectiveness of CAPA's for all systematically occurring product defects. Evaluate shared projects in order to avoid repeating mistakes in future projects.
4. Identify and focus on common success criteria. Focus on the areas of mutual benefit as opposed to the stereotypical commercial inconsistencies in the supplier relation. Areas of mutual benefit include preventing and reducing all loss, focusing on continuous improvement and striving for excellence in quality.
5. Be open and honest in communication by maintaining the partnership; also in cases of quality problems to be hard on the subject but soft on the people. Honor confidentiality agreements. Perform bilateral performance evaluation on common projects and maintain responsibility, reliability and accountability in all we do.
6. Finally, acknowledge and celebrate good performance.

Conclusion

The market of primary packaging materials is shifting from being a more or less commodity market towards being a specialized market with customized products and high quality requirements and expectations.

The relations between pharmaceutical companies and suppliers of primary packaging materials will benefit from a change from a stereotypical customer/supplier relation toward a partnership relation.

Embedded Defects: Strains in the Glass

Glass containers offer several illustrative examples of embedded defects. This author served on PDA's Glass Defects Task Force, which produced *Technical Report No. 43, Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing* in 2007. Two types of embedded glass defects are discussed below.

- Embedded defects like micro cracks and residual stresses in glass containers are defects that may lead to glass breakage later in the lifecycle during subsequent processing steps.
- Glass as a material has a brittle nature in adherence with Griffith's Theory. Griffith's Theory states that breakage propagates if it is energetically favorable. The theory further explains the amount of energy required for breakage propagation is inversely proportional to the depth of the surface flaw.
- In order to prevent embedded micro cracks and residual stresses and subsequent breakages, all glass-to-glass contact, as well as impacts or stresses to the glass, must be observed and avoided rigorously throughout the entire lifecycle of the glass, as the propagation of breakage is progressive and irreversible.
- Glass flaking is another example of an embedded glass container defect. Flaking is a delamination of the glass surface and reveals itself as suspended particles in the drug preparation. The origin of the flakes is alkali borates formed by alkali (e.g., sodium) that has migrated to the surface, evaporated and recondensed on the glass surface.
- There are multiple contributing factors to the formation of flaking: converting speed and converting temperature, annealing conditions, ammonium sulphate surface treatment and eventually the pH value of the drug preparation. Each of these contributing factors must be observed rigorously to avoid flaking in the finished drug preparation.

Pharmaceutical companies that consider quality as a strong competitive parameter are challenged to team up with the best suppliers, i.e., the suppliers that have demonstrated the strongest commitment to quality.

The pharmaceutical companies must strive to be the most attractive or preferred customer and partner in quality. This will enable the pharmaceutical company to achieve, and remain in the most optimal position in relation to the best suppliers of primary packaging materials.

About the Author

Mads Espersen has been with Novo Nordisk for the past 14 years. For the last eight years, Mads has served as the responsible person for the quality of primary packaging materials made of glass. The responsibilities of this position include the assessment and approval of new suppliers as well as regularly and ad-hoc auditing and continuous quality improvement in relation to approved suppliers. Most recently, he has been involved in the uniform implementation of a corporate quality strategy towards suppliers of GMP materials. Mads holds a Bachelor degree in Electronic Engineering from Aarhus Technical University with an emphasis in Medical Engineering.

Commentary: A Chance for Harmonization?

Cold Chain Management in the Inspector's Focus

Rico Schulze, Regierungspraesidium Dresden

Time flies. Only a few months ago, at the *2008 PDA Pharmaceutical Cold Chain Management Conference* in Bethesda, Md., the pharmaceutical industry, solution providers, regulators, and scientists talked about the need for harmonization to ensure product quality worldwide. On May 13, on a larger scale at the meeting of the Transatlantic Economic Council, the U.S. FDA, European Commission, and the EMEA discussed chances for a deeper cooperation in the scope of pharmaceutical regulation. From the industry's standpoint, harmonization is an important issue. Companies operating in different markets have to be aware of different national regulations and need to fulfill varying expectations on quality systems that can cost a lot. So, any harmonization can lead to a more efficient manufacturing and distribution and, finally, to safer drugs.

In those days, pharmaceutical manufacturers—particularly the large pharma companies—did an excellent job establishing good handling criteria and standards for their temperature-sensitive products within their own facilities and in their shippers' hands. During regulatory inspections, many of these sites were not only found highly compliant with the existing regulations, they typically were going beyond what the regulations asked. The drug manufacturers heightened the regulatory authorities' awareness about cold chain management issues and helped facilitate the development of the European regulations, which improved drug safety. This situation hasn't changed. Most manufacturers are setting trends now as ever and are highly compliant.

Wholesalers and retail outlets typically do not adhere to the tightest cold chain management standards, and the knowledge gap between them and the pharmaceutical manufacturers is great.

Relating to Good Cold Chain Management Practice—a topic becoming more and more important—for quite some time there was a little harmonization between the United States and Europe. About three or four years ago when we started to carry out inspections for cold chain management, the United States already had somewhat clear and helpful regulations and recommendations; we didn't. We had our EU GMP Guide and our Guidelines on GDP of Medicinal Products, but these don't give details. They'll tell you what, but not how-to-do. And, finally, these documents aren't dealing with Good Cold Chain Practice.

Unfortunately, problems were (and remain) further down the distribution channel. Wholesalers and retail outlets typically do not adhere to the tightest cold chain management standards, and the knowledge gap between them and the pharmaceutical manufacturers is great.

Even leading German wholesalers have looked overstrained with "Good Cold Chain Management." In my own experience, responsible persons of such companies have asked me what I meant when talking about elements like temperature mapping. So, usually, there were a great many investigator findings related to temperature sensitive storage and transportation at wholesalers' plants. The situation only underscores the need for "Good Cold Chain Management" throughout the whole supply chain.

The usual findings were:

- No temperature mapping
- No or inadequate temperature monitoring records
- Uncalibrated temperature monitoring devices
- Lack of or inadequate written procedures
- Unqualified alarm systems
- Inadequate handling of deviations
- Lack of process qualification
- Suitability of vehicles has not been shown

Of course, these were not only problems of the wholesaling companies. Pharmacies were also a problematic part of the supply chain.

continued on page 28

About the Author

In 1995, Rico Schulze became a registered Pharmacist and graduated with an additional degree in Economics in 2000. Between 1995 and 2001, he worked as a dispensing Pharmacist in a hospital and majored in Clinical Pharmacy in 1999. Since 2001, he has been working for the State Authority for the Supervision of Pharmaceuticals in Saxony, Germany. In 2003, he became a GMP Inspector for the Dresden Inspectorate. Currently he is the Head of the German Inspectors' Radiopharmaceuticals Working Group, and a member of the German Inspectors' Expert Group on Quality Systems.

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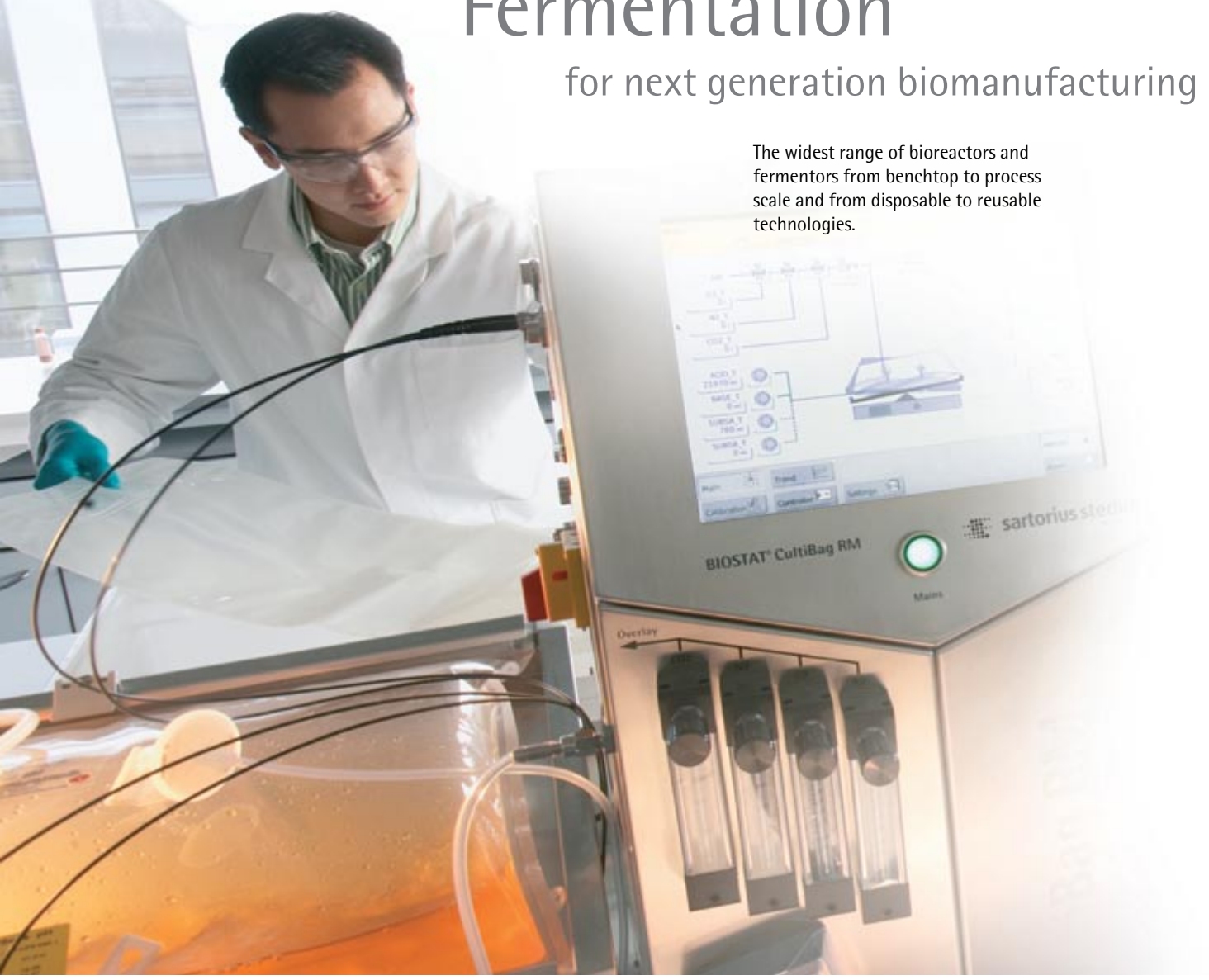

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Perspective: Combating Weaknesses in the Pharmaceutical Supply Chain

Stein Lokstad, Brenntag

The discussion about the safety of medicines has mainly taken place in the framework of counterfeiting. Bearing in mind the heparin case in the United States, we have to widen the focus considering substandard medicines as not only related to counterfeiting, but also related to managing the pharmaceutical supply chain.

In this article, I argue that risks involved in the production of medicines can be reduced by application of existing tools to strengthen the pharmaceutical supply chain.

After the tragic incidents with the use of DEG (Diethyl Glycol) instead of glycerin used as an excipient in medicinal products from the beginning of the 90's in Nigeria (1990), Bangladesh (1990-92), Argentina (1992), Haiti (1995-96), India (1998) and Panama (2006) and the accidents that took place in the United States as a consequence of the use of substandard API Gentamicin—one would think that the necessary initiatives to prevent similar "accidents" were taken. The substandard heparin that was imported to the United States earlier this year indicates that this is not the case.

Regulating the Supply Chain

In Europe, the pharmaceutical supply chain is not regulated to the same extent as it is for the food supply chain. The food regulation covers all that happens in the supply chain from and including the farmer and food additive manufacturer to and including the food retailer. The regulatory focus in pharma, has been on the responsibilities of the holder of the marketing authorization and on securing GMP among the manufacturers and distributors of the finished dosage form.

At the end of 2005, the European legislation included the API manufacturers, but only for human medicines. It leaves out veterinary medicines, nor does it cover the distribution and production of excipients, advanced intermediates and raw materials for the production of pharmaceutical starting materials. Therefore, it remains the full responsibility of the holder of the marketing authorization to make sure that all aspects of the process have an adequate level of quality throughout the entire supply chain.

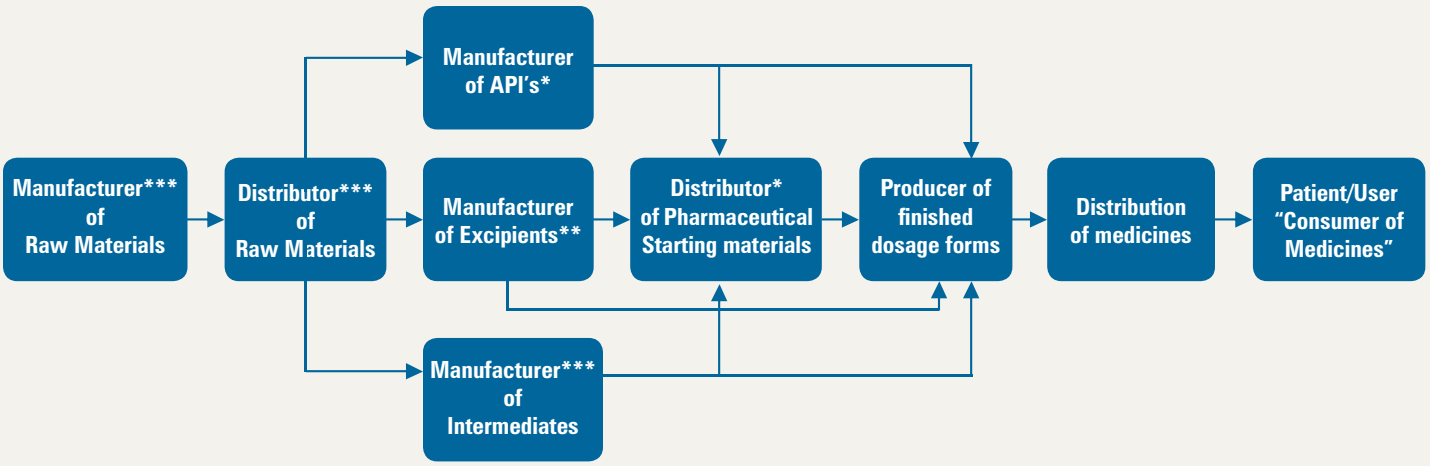
Pharma: Just One Supply Chain

In the European Union alone, there are more than 1200 distributors of chemicals and raw materials. The pharmaceutical industry is global, so when adding these to the number of distributors in China, India, Russia, and the United States, we see that the total number of distributors involved with the pharmaceutical industry is huge. The majority of these companies are specialized in other businesses than pharma, and only a handful can be defined as specialists in distribution of pharmaceutical starting materials.

The same description applies to the manufacturing of starting materials. Few manufacturers of excipients and intermediates are specialized in the requirements of the pharmaceutical industry compared to the total number of manufacturers.

Regulatory coverage of the Pharmaceutical Supply Chain

Adequate QA and QC requirements	Adequate QA and QC requirements	Direct & Indirect GMP / GTDP requirements	Direct & Indirect GMP / GTDP requirements	GMP Pharmaceutical Manufacturing	GDP Wholesale	GDP Retail



* WHO GTDP, EU GMP Part I, IPEC Guideline & ESAD
** WHO GMP, IPEC Guideline & Indirectly through EU GMP
*** Indirectly through EU GMP = responsibility of the holder of the marketing authorization

As such, we cannot take for granted that a simple issue like batch management is known, much less that the meaning of terms like change control and cross contamination are understood. In other words, the challenge to make sure that all steps have adequate quality is huge. Especially when taking into account the different levels of quality, education, and practices in the various countries that form part of the chain and a want of support from the regulatory authorities. The complexity has been very well described in an article published in May 2007.[1]

Available tools

Are there available tools or are we left to each developing tools by ourselves? As APIs are currently covered by the EU legislation, see EU GMP Part I, Part II, Annex 1, I shall focus on areas not covered.

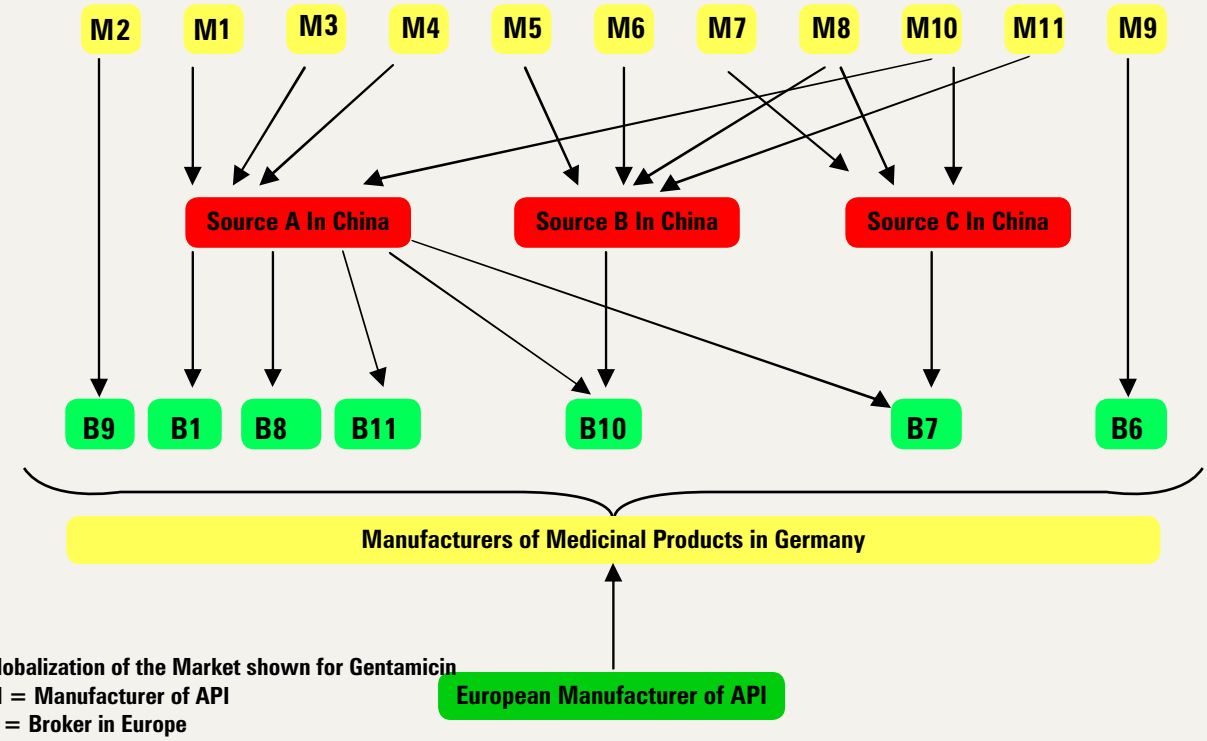
A lot of work has been done. The industry is aware of the weaknesses in the supply chain. Many organizations and people are eager at contributing to securing safe medicines for people, not only in the western world but globally, regardless of the purchasing power of people or countries.

The World Health Organization developed the GMP for excipients and GTDP (Good Trade and Distribution Practices)[2] for distributors of pharmaceutical starting materials, which were intended as a help to comply with global standards in the pharmaceutical supply chain. The International Pharmaceutical Excipients Committee (IPEC) developed a GMP guideline for the manufacturing of excipients, and a GDP guideline for the distribution of excipients[3]. Whereas the WHO documents provide the general principles of good practices expected in the supply chain of excipients and other pharmaceutical starting materials, the complimentary IPEC document outlines a practical approach.

In parallel with the above, The European Chemical Industry Council, and The European Association of Chemical Distributors,[4] developed the European Single Assessment, Document, ESAD. ESAD is a safety and quality assessment system for chemical distributors.[5] It is a joint initiative between Europe's chemical manufacturers and distributors meant to develop and oversee a voluntary system for assessing the health, safety and environmental standards of distributors' operations whilst simultaneously providing a third party assessment system for the distributors' compliance with their Responsible Care program. The appendixes F/G

The Gentamicin Roadmap

A good example of the complexity of the modern pharmaceutical supply chain is that for the antibiotic solution gentamicin. Currently, China is one of the top producers of the active ingredient. The figure below illustrates the roadmap for gentamicin, beginning with raw materials. The figure was presented by Dietrich Schnädelbach, PhD, Federal Institute for Drugs and Medical Devices (Germany), at a meeting with the committee for Good Trade and Distribution Practices in Brussels May 2005. The figure was modified from a version originally developed by a team of German scientists at the University of Würzburg led by Professor Ulrike Holzgrabe, PhD. This team developed the figure for presentation at the 6th APIC/CEFIC European Conference on APIs in Budapest in 2003.



Globalization of the Market shown for Gentamicin
M = Manufacturer of API
B = Broker in Europe

of ESAD, synthesize the WHO GTDP Guideline with the GDP from IPEC. Distributors who have passed the assessment are expected to comply with pharmaceutical industry standards for starting materials. Thus, ESAD goes far beyond the intention of its founders. It is an excellent tool for the distributors, and when a distributor has passed the assessment, it gives evidence to the pharmaceutical industry that the distributor understands his role in the pharmaceutical supply chain.

In other words, there are tools available intended to make the entire pharmaceutical supply chain work smoothly, even when the chain consists of companies from a wide variety of countries, business cultures and product orientations. No one said it is easy to make sure that every link in the chain is adequately strong in quality terms; but it is not as difficult as it would have been if it was not for the people that predigested a voluminous quantity of material to simple application oriented guidelines and documents as the ones mentioned above.

The risks involved in the production of medicines can be reduced by applying these tools in order to ensure the right choice, when looking for partners and suppliers. The effect will be a professionalized pharmaceutical supply chain we all can be proud of.

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About the Author

Stein Lokstad has been at Brenntag since 1997 as Divisional Manager for the pharmaceutical activities in Denmark. As the European facilitator, he established and monitored the implementation of the Brenntag pharma strategy in Europe. He became the Business Unit Director with full P/L responsibilities for the distribution of pharmaceutical starting materials and cosmetics ingredients in the Nordic Region, as well as the production and global sales of adjuvants to the vaccine industry until 2007. As of 2008, Stein assumed the role of General Manager of the Brenntag Biosector, the leading manufacturer of adjuvants for vaccines.

He was the chairman for the Good Trade and Distribution Committee in both the European and the International Federation of Chemical Distributors (FECC and ICCTA) from 2003 to 2006. As such, he was spokesman on behalf of the industry towards industry associations, EU and WHO.

Commentary: A Chance for Harmonization?, continued from page 24

From my point of view, this unsatisfactory situation wasn't just a German phenomenon. I suppose that we could find more or less the same problems in many other European countries, too.

The situation improved rapidly. Sure, this has something to do with a lot of helpful documents written by regulators and accepted by all parts of the supply chain. In the UK, MHRA published a document entitled, *Recommendations On The Control And Monitoring Of Storage And Transportation Temperatures Of Medicinal Product*s, and in Ireland, the Irish Medicines Board published one entitled, *Guide To Control And Monitoring Of Storage And Transportation Temperature Conditions For Medicinal Products And Active Substances.*

Now, these documents are a base for inspections—sometimes even in other European countries, and they are at least a little more known to wholesalers and pharmacists. Also used are PDA's *Technical Report No. 39, Revised 2007, Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products Through the Transportation Environment,* or Chapter <1079> from the USP "Good Storage and Shipping Practices."

The improved situation also has to do with the fact that Cold Chain Management became a more and more important part of our inspections. But still we didn't reach our goals. From time to time, we can find more important or even critical deficiencies, failures and ignorance. Regarding the possible consequences—each of them is too much.

When discussing at the PDA conference on Good Cold Chain Practice in Berlin, Germany, November 4-5, we all should keep in mind what can happen when things go wrong. In view of new and extremely valuable and sensitive products, in view of global markets, we should keep in mind the increased importance of the whole supply chain in the future. And we should search for solutions what we can do to make this supply chain safer. In my eyes, that's true harmonization. Hang on! And Welcome to Berlin!

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Quality & Regulatory Snapshot

In *Print*

The Cost Of Quality

Chapter 8 from Risk-Based Compliance Handbook *by Siegfried Schmitt, a recently published PDA-DHI book. Go to www.pda.org/bookstore for more information. References from this excerpt have been removed, but are available in the book.*

Not unexpectedly, benchmark data on the cost of quality (CoQ) is not readily available, mainly due to the fact that few companies have implemented systems that would permit reasonably accurate estimation of the CoQ. In a recent article it was estimated that up to Euro 140bn of annual global pharmaceutical sales are subject to some form of economic evaluation, which in itself is a key driver for industry to drive cost efficiency in its operations.

Where measures such as establishing a risk-based compliance approach result in additional cost, the added expenses must not outweigh additional benefits, or costs must have to be lowered elsewhere.

Operations in the healthcare industry are dependent on IT. Of course, driving cost down in this area has been and is the focus of management in all of industry. What is, however, most astonishing—and fascinating and disappointing at the same time—is the extremely high failure rate of IT projects; estimated by some at over 50%. Although there are many (obvious) reasons why projects fail, one should not fail to note the financial perspective, where project costs have been capitalized with a view towards amortization. Cancellation of the project is likely to involve a one-off profit and loss hit of the total costs invested up to that date; a move seldom popular with management. In fact, only a few percent (3% in a study of 1,700 projects were cancelled, while 31% were or were expected to deliver negative net value, i.e., destroyed value.

Where measures such as establishing a risk-based compliance approach result in additional cost, the added expenses must not outweigh additional benefits, or costs must have to be lowered elsewhere.

In the context of cost of quality these are frightening prospects as they affect all stages of the drug lifecycle.

A well-researched article addresses the financial returns on investment from PAT and lean manufacturing. The results of the case study show that it should be possible for a generic pharmaceutical manufacturer to generate savings of up to 6% of revenues through deployment of PAT and lean manufacturing. The authors describe in great detail the model on which they based the gain in revenue, but do not make any assumptions on investment cost. Although only hypothetical, it can be expected that certain cost elements could easily wipe out any expected gains. These costs arise from:

- pre-approval inspection as PAT is introduced
- variation (i.e., post-approval changes) submissions
- IT infrastructure cost to manage PAT data

The time from project initiation to regulatory approval should not be underestimated. This can be any time from one to three years. Industry feedback at PDA and DIA conferences in 2007 indicated a typical two-year project timescale. This makes such project implementation only feasible for long-term investment. Also, many suppliers operate globally, which makes them subject to approval from more than one regulatory agency. Despite the fact that both the EU and the U.S. are encouraging PAT and modern manufacturing methodologies, founded on a risk-based approach, there is as yet no case where approval for a variation has been granted equally by both regulators. Variations submitted to one agency only have, however, been successful. The regulatory risks for industry in introducing PAT may have been significantly reduced as the authors write, but which pharmaceutical company would risk applying these principles to a new drug today? The costs and risks of bringing a new drug to market are prohibitively high even for consideration by pharmaceutical companies. Of course, PAT, as well as lean, six sigma, and other best practice methodologies will bring the potential for cost savings, but it is in the development of new products and processes that maximum benefit can be reaped from them, not in the modification of less than perfect ("fat") processes.

The cost of implementing the new paradigms of ICH Q8, Q9 and Q10 should be counterbalanced by the cost savings achieved through fewer changes and variations, faster time to market and other benefits. A key driver in this scenario is the establishment of quality by design (see ICH Q8), which is considered to bring about much of the expected benefit for industry. It seems this assessment does not take into account the fact that reimbursement of industry by the national healthcare agencies relies almost always on the outcomes of the clinical studies, not the scientific knowledge amassed by the companies. It is certainly prudent to address the three guidance documents individually when assessing benefit/cost and benefit/risk.

It is not unusual to find that the cost of compliance is largely equated to the cost of (extra) manpower, as this is easy enough to calculate. But that is far too simplistic to be of any real value. Projects that aim to implement change typically take a significant amount of time and many of those involved will only be assigned part time or for part of the project. In a recent example, improvements to a Corrective and Preventive Action (CAPA) system were given a five-year timeframe. This length of project permits a continual increase in the benefits that can be achieved—in this case a reduction of 50% in overdue investigations after three years.

A cost of poor quality (COPQ) model was described recently to help drive process improvements. This approach describes the cost of quality as the difference between the actual cost of a product or service and what the cost would be if the processes were effective in manufacturing products that met customer needs and were defect free. COPQ is therefore the sum of costs when the quality system is not perfect. Four elements make up the COPQ:

- cost of external failures, covering all costs associated with addressing defects for products that have left the manufacturer's control
- cost of internal failures includes all costs associated with addressing defects that are identified internally during product development and production
- cost of appraisal covers the costs of inspections to identify defects that occur during product development and production
- cost of preventive actions are all costs associated with a process improvement program

COPQ is a tool that helps identify which preventive actions will offer the greatest opportunities for reducing costs and improving productivity. An element of COPQ is to perform risk assessments, e.g., using the FMEA methodology. The concept can be summed up as: "Quality is free. It is not a gift, but it is free. What costs money are the unquality things—all the actions that involve not doing the jobs right the first time."

A recent document by the Institute for Quality and Efficiency in Health Care (IQWiG) details the approach to finding a common measure of value such as quality-adjusted life year, for example. This attempt to judge the worthiness of one disease over another and the benefits of treating one over the other has not yet resulted in a universally accepted method for doing so. The IQWiG approach is more pragmatic and aims at comparing the efficiency of treatments in a specific therapeutic area. This is a model which could be incorporated into a risk-based approach.

The need to assess the benefits and costs of drugs, and thus implicitly the cost of quality, is also driven by national legislation promoting competition in order to contain cost within the health insurance systems.

At a European inspectors convention, the cost of implementing Quality Risk Management (QRM) (or ICH Q9) was discussed. The consensus was that it is not necessary for a large upfront expenditure to implement a QRM system. There was a general feeling that implementing better QRM will enable cost savings by prioritization of quality efforts by a focus on value-added activities.

From a facilities management perspective, the cost of quality is equated to the monetary loss incurred by not maintaining proper environmental conditions required to sustain product integrity throughout. These could be measured, for example, in lost production time (lost revenue), lost research (extra cost for time to market), lost product (direct cost) and regulatory fines (direct cost). For companies to find a balance between profitability and risk the risk management methodology should provide information on risks in monetary units (financial exposure of the company to specific risks). At the PDA Quality Systems Conference in Dublin in December 2007, Martin VanTrieste (Vice-President, Quality, Amgen) estimated the cost for a non-conformance investigation to be in the range of $1,000 to $25,000 per case.

continued on page 33

Regulatory Briefs

Regulatory briefs are compiled by PDA member volunteers and staff directly from official government/compendial releases. Links to additional information and documentation are available at http://www.pda.org/regulatorynews.

North America

U.S. FDA Seeks Volunteers for QbD Biotech Pilot Program

The FDA is looking for companies to participate in its quality-by-design (QbD) pilot program for biotechnology submissions, which is intended to help the Agency develop a guidance on the topic.

Participants in the pilot program will need to submit quality information for their biotechnology products. Submissions will include BLAs, BLA supplements or NDAs reviewed by the FDA's Center for Biologics Evaluation and Research's (CBER) Office of Biotechnology Products. The submissions should demonstrate an applicant's increased knowledge of product attributes—linking the attributes to process parameters in an expanded change protocol.

The project will explore the use of these protocols to describe the specific tests, studies and acceptance criteria that demonstrate that certain manufacturing changes will not have adverse effects.

U.S. FDA Publishes Draft Guidance on Labeling OTC Skin Drug Products

A draft Guidance for Industry entitled, *Labeling OTC Skin Protectant Drug Products* is now available for comment from the U.S. FDA. The guidance provides recommendations on how to label over the counter (OTC) skin protectant drug products.

Comments are due October 3, 2008

Parametric Release Draft Published by U.S. FDA

The U.S. FDA has published a draft guidance for industry entitled, "Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes."

The draft guidance provides recommendations to applicants on information to include in support of parametric release for sterile drug products terminally sterilized by moist heat when submitting: a new drug application; abbreviated new drug application; new animal drug application; abbreviated new animal drug application; or biologics license application.

Comments are being solicited and must be submitted by October 6, 2008.

New USP Residual Solvents Standards Reinforced in U.S. FDA Draft

The U.S. FDA has published a notice of the availability of a draft guidance entitled, *Control of Residual Solvents in Drug Products Marketed in the United States.*

On July 1, 2008, the USP published a new test requirement for the control of residual solvents; General Chapter <467> "Organic Volatile Impurities" was replaced by General Chapter <467> "Residual Solvents." The FDA draft guidance provides recommendations on how to comply with the USP changes. The change affects all compendial drug products marketed in the United States.

Comments are due to the FDA by October 6, 2008.

U.S. FDA Offers Final Rule, Guidance on cGMP Compliance

The US FDA's final rule amending the cGMP regulations for human drugs, including biological products, to exempt most Phase 1 investigational drugs from complying with the regulatory CGMP requirements has been published. The Agency will continue to exercise oversight of the manufacture of these drugs under their general statutory cGMP authority and through review of investigational new drug applications.

In addition, a guidance document entitled, *Guidance for Industry: CGMP for Phase 1 Investigational Drugs,* is currently available. The Guidance provides assistance in applying relevant cGMP requirements of the FD and C Act to the manufacture of most investigational new drugs, including biological drugs, used in Phase 1 clinical trials. This finalizes the draft guidance entitled, *INDs – Approaches to Complying with CGMP During Phase 1.*

U. S. FDA Establishes Final Rule on NDA's and ANDA's

The U.S. FDA has issued a final rule amending the regulations on New Drug Applications and Abbreviated New Drug Applications. This will discontinue the use of approvable and not approvable letters when FDA takes action on these marketing applications. The Agency will begin to send applicants a complete response letter to indicate that the review cycle for an application is complete, and that the application is not ready for approval.

FDA is also revising the regulations on extending the review cycle due to the submission of an amendment to an unapproved application. The Agency will start a new review cycle after the resubmission of an application following receipt of a complete response letter.

Finally, FDA is adding provisions on the issuance of complete response letters to the biologics license application regulations. It has indicated that the changes are being made to implement the user fee performance goals referenced in the Prescription Drug User Fee Amendments of 2002 that address procedures and establish target timeframes for reviewing human drug applications.

In Print, The Cost of Quality, continued from page 31

The integration of risk and drug safety management in a proactive manner is a very new concept. One factor holding back the development of such a system is the inability to determine if the investments in such a model will provide any benefits and generate returns on investment. There are, however, examples of successful integrated safety and risk management as shown by the relaunch of thalidomide by Celgene. Although there still may be no model that helps predict the business benefits of such an integrated approach with any great degree of accuracy, there can be no doubt that by implementing it companies will have a competitive advantage.

Non-conformance affects the share price of listed companies, and has a general effect on sales, as exemplified by a 10% drop in Schering-Plough's sales and a drop in the share price from $60 per share to $24.75 per share after entering into a consent decree.

The concept of a risk-based approach still is far from being generally considered and adopted into best practice business models. For example, a paper describing an approach to world class manufacturing lists the following seven activities:

- reduce lead times
- speed time-to-market
- cut operations cost
- exceed customer expectations
- manage the global enterprise
- streamline outsourcing processes
- improve business performance visibility

Clearly, this list is looking at the business environment from a cost perspective, but crucially misses to apply risk management. All too often cost reduction activities have resulted in shortcomings on the compliance front, and have ultimately led to higher overall costs due to regulatory actions.

Similarly, the University of St. Gallen in Switzerland conducted a benchmark study of API manufacturers to establish what constitutes operational excellence from a cost perspective. Four critical areas were identified:

- increase in flexibility
- improvement of quality
- increase of service levels
- reduction of costs

Several methodologies applied by industry are listed, such as total productive maintenance, total quality management and just-in-time, but it is unclear if risk management is at all part of any of these approaches to cost control.

The American Society for Quality has launched an initiative called, "Making the Economic Case For Quality." A key message is that the benefits from quality management are achieved over a long period and, even after effective implementation, it still takes a few years before financial performance starts to improve. When improvements are only incremental, i.e., only save little time or create small amounts of extra revenue, too many organizations mistakenly conclude that neither the improvement nor the analysis would be worth the effort.

Volunteer Spotlight

If you read it in the PDA Letter or the PDA Journal or hear it through PDA, it is probably acceptable to the regulators.

Karen Ginsbury

President and Owner, PCI Pharmaceutical Consulting Israel Ltd.

Education: Bachelor of Pharmacy, School of Pharmacy, University of London
Master of Science, Microbiology, Birkbeck College, University of London

PDA Join Date: 1990

Areas of PDA Volunteerism:

PDA Israel Chapter (co-founder and past president)
RAQC (member)
Task forces to comment on guidance in the making (member)
Conference speaker
Program planning committee for Investigational Products Conferences in Lyons 2007, Paris 2008, and Rome 2009 (member)
Task Force on GMPs for Investigational Products (co-chair)

Professional Awards Won:

IVT presentation of the year 2006 and web seminar of the year 2007.

Why did you join PDA and start to volunteer?

I joined PDA because my boss at the time told me that PDA was the only not-for-profit professional organization whose opinions could be trusted without additional verification. In other words, if you read it in the *PDA Letter* or the *PDA Journal* or hear it through PDA, it is probably acceptable to the regulators. My experience has been that he was absolutely correct.

I started to volunteer when I realized it was a way to directly influence the making of regulations and guidances, while at the same time enriching my personal knowledge base, networking and meeting friends and colleagues. Over the years these different reasons have coalesced so that PDA has become almost like a family in that I receive professional support and friendship from it.

Of your PDA volunteer experiences, which stand out the most?

Commenting on the first OOS guidance. It was a very short timeframe, but very important to the Israel Chapter. We just got together (three of us) at the end of one day and did it—four hours straight of comments. Much more recently, as a member of PDA's Regulatory Affairs and Quality Committee (RAQC), reviewing the comments on Annex 2 of the EU GMPs, which is a lengthy and very important document that a group of PDA volunteers must have put in hours and hours of work.

How has volunteering through PDA benefited you professionally?

It has allowed me to stay current. Remember the little "c" before GMP? Well the pace of regulation review and updating in a global environment is hectic. We have all bookmarked "what's new" on the EMEA and U.S. FDA websites, or even get the automatic e-mails, but who has time even to download the guidances? In RAQC you are expected to vote on any comments that PDA sends the regulators to draft regulations and guidances. At the end of it, you know what is going on and you have learned the guidance.

Which PDA event/training course is your favorite?

I am somewhat biased because I love the field of investigational products, which is a growing field of interest. We have already done two very successful conferences and are in the advanced planning stages of the 2009 conference in Rome. Also, the PDA/EMEA Joint Conference in Budapest in February was of huge value.

What would you say to somebody considering PDA membership?

If you work in the pharmaceutical/biotech/API industry you need to be a member of PDA. I don't see any other professional group that provides the same or similar opportunities to advance your learning and keep informed. Time is a precious resource and as I see it, PDA saves its members time where it counts the most—in continuing education and therefore, continual improvement.

Volunteer Spotlight

Michael N. Eakins, PhD

Founder and Principal Consultant, Eakins & Associates

Education: BSc (Hons), Physiology and Zoology, University of London
PhD, Physiology, University of London

PDA Join Date: 2003

Areas of PDA Volunteerism:

2004, 2005, 2006 Annual Meeting Program Planning Committee (member)
2007 Annual Meeting Program Planning Committee (chair)
2006, 2007 Universe of Pre-filled Syringe Program Planning Committee (member)
2006, 2007 Pharmaceutical Anti-Counterfeiting Forum Program Planning Committee (chair)
Glass Defects Task Force (member)
Glass Defects Task Force for Ampoules, Syringes and Cartridges (co-chair)
Program Planning Board (member)

Why did you join PDA and start to volunteer?

Most of my career in the pharmaceutical industry has been on the drug development side, so joining the PDA was a natural fit. I joined rather late in life simply due to not having the time to dedicate to PDA while being responsible for a drug development department, and later on due to a job that required commuting to and from Europe on a regular basis. However, once I started my own consulting company joining PDA was one of my first actions. Having joined, I was not about to just sit on the side lines, but I was determined to lend a hand by volunteering. My first experience in this regard was on the program planning committee for the Annual Meeting that was held in Orlando in 2004. Not perhaps the most auspicious of starts, but it was a very useful learning experience.

Of your PDA volunteer experiences, which stand out the most?

Opening the Annual Meeting in Las Vegas in my role as Chair of the Program Planning Committee in 2007. What could be better in life than to be on stage with a microphone in front of a large expectant audience in Las Vegas. Priceless!

How has volunteering through PDA benefited you professionally?

Through making new contacts at meetings and being recognized as an expert in both glass and plastic pre-filled syringes and anti-counterfeiting technologies by giving presentations at PDA's conferences dedicated to these topics and being a session moderator at numerous conferences. In addition, there is always something new to learn at these conferences both in the conferences themselves and via the Interest Groups. The Packaging Science Interest Group is another excellent forum for discussion for me.

Which member benefit do you most look forward to?

While keeping up-to-date in the latest science in my fields of interest by attending PDA conferences is important, I think that I really look forward to being able to interact with the speakers and the attendees and exchanging ideas and experiences.

Which PDA event/training course is your favorite?

My two favorites are the pre-filled syringe and the anti-counterfeiting forums, because I was closely involved with the recent conferences, both as an organizer and as a speaker. The topics are linked in that each involve primary packaging. In the case of anti-counterfeiting, the primary packaging is where the anti-counterfeiting and track and trace technologies will be placed.

What would you say to somebody considering PDA membership?

Join of course. However, do not just join but get directly involved in one of the activities at both the headquarter and chapter level. PDA depends on volunteers to bring their knowledge and organizing skills to organize scientific meetings, identify key speakers and serve on committees that develop the Technical Reports. New ideas and insights are always welcome.

Once I started my own consulting company joining PDA was one of my first actions.

Please Welcome the Following Industry

Ashley Ahmed, Genentech

Afzal Ali, Sanofi Pasteur

Frank Alicea-Rivera, Wyeth Pharmaceutical

Hortense Allison, Bausch & Lomb Pharmaceutical

Nicole Amenkowicz, Genentech

Mahindra Anmolfingh, Sanofi-Aventis

Degraft Botah Appiah, Mataheko Pharmacy

Edward Armstrong, Genzyme

Preben Astfeldt, Novo Nordisk

Paul Auric, Genentech.

Evan Bakst, Tremblant Capital Group

Kandi Barnhart, USAMMA/DOC

Carol Basey, Genentech

Prabir Basu, NIPTE

Hans-Guenther Bauer, Boehringer Ingelheim Pharma

Jacqueline Berretta, Boston Scientific

Robert Bishop, BMS

Forrest Blair, Thermo Fisher Scientific

Albine Blanche, Watson Laboratories

Christopher Bogart, Bayer

Jeremy Bond, Sanofi Pasteur

Eric Borin, BD Medical

Michael Bosbach, Procter and Gamble

Ashley Brauer, Exoxemis

So-ching Brazer, MedImmune

Scott Brown, Schering-Plough

Cheryl Brucato, Wyeth

Kathy Burg, CV Therapeutics

Jerry Cacia, Genentech

Ying Cai, Gilead Sciences

Jason Cameron, Genzyme

Christine Cantarino, Abbott Laboratories

Jean-Pol Cassart, GlaxoSmithKline Biologicals

Marco Cerri, Kedrion Spa

Katherine Chaloupka, Amgen

Andrew Chang, PharmaNet Development Group.

Vandana Chauhan, Genentech

Ashok Chetty, Dupont

William Cholish, Sanofi Pasteur

Ming Ying Chong, Clearlab SG Pte

Ju-Yu Chung,

Young Kuk Chung, Yung Jin Pharm.

Orla Cloak, Lonza

Thomas Coady, Inspire Pharmaceuticals

James Cohen, Buchanan Ingersoll & Rooney

James Copp, Targanta Therapeutics

Sue Cranfill, Eli Lilly

Jay Crespo, Applied Biosystems

James Dacek, Steris Corporation

Kairus Dadachanji, Kaisha Manufacturers

Bruno Darrah, Draxis Pharma

Dominique David, ASSYSTEM

Eric De Hennezel, Nypro Healthcare

Guy De Jane, Amgen

Chris DelGiudice, Becton Dickinson

Jens Demand, Novartis Pharma

Kaat DeMoor, Nobilon

Michael Dempsey, Cook Pharmica

Mo Derakhshan, SAFC Pharma

William Devine, Pharma-Tech Services

Joe Donovan, Millipore Corporation

Shaun Downes, Novartis vaccines and Diagnostics

Trevor Downey, Genemedix

Inger Drengsgaard, NNEPharmaplan

James Drob, Sanofi Pasteur

Rhona Duane, Irish Medicines Board

Brenda Dukeshire, Millipore

William Ellis, IVX Animal Health

Shane Ernst, DSM Pharmaceuticals

Gene Espinosa, Genentech

Hiroki Etoh, Senju Pharmaceutical

Joe Fairfield, Baxter Healthcare

Jill Feldman, Ferro Pfanstiehl

Daniel Fishman, Boston Scientific

Edel Fitzmaurice, E. Fitzmaurice and Associates

Eileen Flynn, Genentech

Karen Flynn, West Pharmaceuticals

J S Forney, Baxter Healthcare

Karl Fournier, Covidien Imaging

Tony Gabriele, Rexam

Adil Gatrad, Watson Pharmaceuticals

Denise Gavin, FDA

Gerald Geisler, Bristol-Myers Squibb

Markus Gemuend, Genentech

Carlo Gherardi, TUV Italia

Karen Ghys, Schering-Plough

Chris Glaeser, Baxa Corp

Norman Goldschmidt, Bristol-Myers Squibb

Rachel Golinsky, Sanofi Pasteur

Renee Greenwalt, Limited

Gert Jan Haan, Centocor

Peter Habura, Forest Laboratories, Inc

Patrick Haffey, Hollister-Stier Laboratories

Kheira Hamadi, Sanofi Pasteur

Aimin Han, Shenzhen Hepalink Pharmaceutical

Leaders to the PDA Community

Deborah Harrison, Dey

Ben Hayman, GSK

John Henstrand, BioMarin Pharmaceutical

Herman Herz, Novo Nordisk

Denton Hickey, Alcon Research

Sone Hiroyuki, Hitachi

Donald Hong, Covidien

Jessica Hopwood, Ipsen Biopharm

Chris Howard, BTF

Arwel Hughes, Novartis Vaccines & Diagnostics

Kazumi Inoshita, BIKEN

David Istance, Genentech

Raquel Iverson, Genentech

Kazutaka Iwakawa, Applied Biosystems Japan

Melanie Jackson, APP Pharmaceuticals

Daniel Janssen, 3M

Huang Jaujie, Bureau of Control Drugs Department of Health

Ron Javier, CBL

Hanne Jensen, Symphogen

Jessica Kahle, Afton Scientific Corp

Umesh Kapre, Sequent Scientific

Yuji Kawamoto, Astellas Pharm

Sam Kee, CSL Biotherapies

Meera Khullar, Hospira

Ghee Kim, Sangart

Kathryn King, FDA

Sophia Koutoulas, Biogen Idec

David Kunzinger, Procter & Gamble Pharmaceuticals

John Kyranos, Shire

Aline Le Breton, BD

Brendan Lee, Tremblant Capital Group

Robert Legros, Ecole Polytechnique

Laura Lei, Baxter

Monica Lent, Genentech.

Chi-Chou Liao, Department of Health - The Executive Yuan

Deborah Lindstrand, Baxter Healthcare

John Linfante, Excelsior Medical

Tammie Logan, Chesapeake Biological Laboratories

Kelly Lorenz, BD Diagnostic Systems

David Lowry, Parexel International

David Lue-Chee-Lip, Sanofi Pasteur

Benjamin Mabile, GlaxoSmithKline Biologicals

David Mackey, Genentech

Yutaka Maki, Astellas Pharma Inc.

Anthony Mallas, Xcellerex

Thomas Manley, MassBiologics

Ruth Mantle, Parker Hannifin

Ruben Martinez, Excelsior Medical

Monika Masternak, CIBA Vision Sterile Manufacturing

Abdul Mazid, Bayer Pharmaceutical

Kristine McCarthy, Wyeth BioPharma

Anna McCartney, Sanofi Pasteur

Anne McCasland-Keller, Eli Lilly

Justin McCullough, Johnson and Johnson

Manita Mehmi, Aston University

Jeannie Metzinger, Colorcon

Johnny Mikell, UCB

Brian Miller, Transave

Mark Miller, Applied Biosystems

Jay Millwater, AAI Pharma

Juan Luis Minana Figueres, Lonza Biologics

Manabu Miura, Daiichisankyo

Sigal Molgan, Teva Pharmaceuticals Industries

Jang Ho Moon, Penmix

Stephen Morley, Getinge Infection Control

Chris Morrisey, STERIS Corporation

Jaclyn Moxham, Pfizer

Meghan Murphy, FDA

Joseph Murray, Afton Scientific

Amit Nag, Hach Ultra Analytics

Fumitomo Nagai, Central Bussan

Robyn Neitzschman, Dyax Corp

Cynthia Newth, Acadia Pharmaceuticals

Patricia Neysens, Tigenix

Liem Hoang Nguyen, Amgen

Huong Nguyen, Bayer

Kim Ngan Nguyen, GlaxoSmithKline

Phung Thien Nguyen, FDA

William Nichols, Parexel International

Mary Nicholson, Sanofi Pasteur

Matt Nicoll, Glaxosmithkline Biologicals

Laura Noguera, Grupo Reig Jofré

Fergal O`Donovan, Schering-Plough

Bridgett O`Shea, Wyeth

Caroline Ocasio, Wyeth

Olumuyiwa Odebode, Iva Pharmamed

Birthe Olsen, Novo Nordisk

Joseph Oppong, Mataheko Pharmacy

Jaime Ortega, Tecnyca

We welcome more of this month's new PDA members on the next page ➤

Please Welcome the Following Industry Leaders to the PDA Community

continued from previous page

Thomas Otto, Vetter Pharma-Fertigung

Dawn Palmer, Amgen

Thoralf Petzold, Octapharma

Karl Pflanz, Sartorius-Stedim Biotech

John Phan, APP Pharmaceuticals

Brenda Pillaria, FDA

Landon Piluso, Baxter

Paul Pinheiro, Cibavision

Mark Piscatelli, Biogen Idec

Milena Pisek, Lek Pharmaceuticals

David Popp, GBI

Catherine Porterfield, Afton Scientific Corp

Geoffrey Pot, Baxter

Maria Eugenia Provenzano, Syntex

Ussma Quraishi, SNC Lavalin Pharma

Mark Rabideau, Bristol Myers Squibb

Ali Rahman, Althea Technologies

Navneeta Rajan, Baxter

Lisa Randle, Nutramax Laboratories

Andrew Randolph, Baxter Healthcare

Susan Reid, Irish Medicines Board

Elizabeth Reynaga, Sage IVF

Jeff Rice

Douglas Rich, Amgen

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Award Winners Acknowledged at Delaware Valley Chapter Event

Susan Vogt Speth, Chapter Operating Committee Member (ret. GSK)

The PDA Delaware Valley Chapter sponsored an educational evening on June 17, at the Desmond Hotel and Conference Center in Malvern, Pa., attended by 130 participants from area pharmaceutical and biopharmaceutical industries.

During this meeting the Delaware Valley Science Fair Finalists presented their projects and were honored with awards presented by **Traute Ryan**, PDADV Student Committee Chair. The student winners were:

- **Sourav Sinha** (12th grade) for "Identification of Bacterial Species using PCR Assay with Novel Fluorogenic Probes"
- **Curtis McKittrick** (12th grade) for "What is the Effect of Cranberry Proanthocyanidins on the Rate of Formation of S. mutans Biofilms"
- **Cristy De Obaldia** (11th grade) for "Treatment with Antisense PSODN in Mycobacterium smegmatis Enhances Antibiotic Sensitivity"
- **Raina Jain** (9th grade) for "Proliferation of Cells on Bioactive Glass"
- **Benjamin Song** (9th grade) for "Does DNA Damage Accumulate in HSV DNA with the Time of Latency?"
- **Puja Upadhyay** (7th grade) for "The Effect of OTC Children's Cough Medicine on the Heart Rate of Daphnia"
- **Aviana Duca** (6th grade) for "All Washed Up – And Then Some"
- **Rita Marino** (6th grade) for "Hands or Floor? Bacteria Galore!"

Following the students presentations and awards, participants were further educated with a presentation on worldwide product labeling presented by **Barbara Fanelli**, Associate Vice President, Regulatory Labeling, Sanofi Aventis.

Barbara's lecture included a discussion on the development of worldwide product labeling and how labeling development parallels the drug development process. She described how good labels incorporate the required information about the safe and effective use of the product, and in some cases include usage for treatment against other indications.

Barbara also provided an overview of the labeling requirements in the major regions, e.g., United States and the European Union, showing similarities and differences between the regions. She concluded with her analysis of some recent changes in regulations and their impact on labeling. At the close of her presentation, Barbara entertained questions and shared ideas with the attendees.

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[1] Rose, Bonnie E. 2001. Isolation and identification of *Salmonella* from meat, poultry, and egg products in Microbiology laboratory guidebook, 3rd ed., Food Safety and Inspection Services, U.S. Department of Agriculture, Washington, D.C.

[2] U.S. Food and Drug Administration. 2003. Bacteriological Analytical Manual (online), AOAC International, Gaithersburg, MD.

[3] International Organization for Standards (ISO). Microbiology of food and animal feeding stuffs – Horizontal method for the detection of *Salmonella* spp., 4th Edition, ISO 6579:2002.

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Microbiologists, Prepare to be Wowed at PDA's 3rd Annual Micro Conference

Chicago, Ill. • October 20–22 • www.pda.org/microbiology2008

Michael Miller, PhD, Eli Lily and Brenda Uratani, PhD, U.S. FDA

PDA's 3rd Annual Global Conference on Pharmaceutical Microbiology offers an excellent opportunity to hear, meet and interact with your fellow microbiologists and leaders in pharmaceutical microbiology. This year's conference theme is: *The Role of Microbiology in Delivering Quality Products*.

There have been exciting new technological advances in microbial identification (ID) systems designed for the pharmaceutical industry. The conference will bring together a number of global experts on this topic in an exciting discussion panel. **Jaspreet Sidhu**, PhD, VP, Business Development, Molecular Epidemiology, will be presenting a polyphasic approach to microbial ID using sequencing of ribosomal RNA genes and other specific genes, combined with classical phenotyping methods, providing a clearer match for bacterial and fungal classification. **Mareike Wenning** PhD, Scientist, Technical University Munich, will present Fourier-transform infrared (FTIR) spectroscopy, a whole organism fingerprinting technique based on the adsorption of infrared light by different biochemical components that make up microbial cells. We will also hear from **Colin Dykes,** PhD, Chief Scientific Officer, OpGen, on whole genome optical mapping which provides high resolution DNA based identifiers capable of identifying microorganism to the species, subspecies, strain or isolate level. There will also be an update from **Chris Pitulle,** PhD, Senior Field Applications Specialist, Applied Biosystems, on comparative rDNA sequencing as a rapid and accurate means for microbial ID even when a pure culture is not available and **Andrew Bartko**, PhD, Principal Scientist, Battelle, will speak about a novel spectroscopy-based microbial identification platform. What is most exciting is that you will hear examples of practical applications of these new technologies under pharmaceutical microbiological settings.

Do you ever assess whether microorganisms from different sources (e.g., ATCC, NCTS, NCIMB) that are used during compendial testing are interchangeable or equivalent? You will hear from **Tony Cundell**, PhD, Director, Pharm. Sci. , Schering-Plough, on this very interesting topic.

> ***The conference will bring together a number of global experts on this topic in an exciting discussion panel.***

Regulatory agencies have been advocating the importance of risk assessment and science based approaches to achieve product quality. In this conference, you will hear real life case studies where quality risk management is employed in manufacturing, the application of QbD and QRM (Quality Risk Management) from the industry. You will also be introduced to interesting examples on media fill designs to accommodate campaign manufacturing and different approaches used to control cross-contamination in biotech manufacturing facilities.

Scientific knowledge derived by basic research is the corner stone for pharmaceutical microbiology. During this year's conference, you will interact with subject matter experts on a variety of scientific levels:

Understanding of the mechanisms of killing and resistance of bacterial spores is important in sterilization validation and manufacturing control strategies, as well as the proper use of biological indicators. We are honored to have **Peter Setlow**, PhD, Professor, University of Connecticut Health Center, talk to us about the biochemical aspects related to the inactivation of spores.

Understanding the scientific principles for how environmental monitoring devices operate is essential in setting up a robust manufacturing control strategy. Monitoring devices are designed differently, and the principles on sampling efficiency (for these devices) are often neglected. **Bengt Ljungqvist**, PhD, Professor, Royal Institute of Technology and **Berit Reinmuller**, PhD, Senior Researcher, Royal Institute of Technology, will provide us with an in-depth discussion on this topic.

This year's conference offers an excellent opportunity to hear first hand global compendial and regulatory perspectives, with speakers representing the United States and European Pharmacopeias, U.S. FDA, MHRA and other European regulatory authorities. We are confident that you will benefit by listening to talks by regulatory authorities from both from FDA and EU on a variety of topics, including inspectional issues and trends relating to pharmaceutical microbiology.

For more information and to register for this important and informative conference, visit www.pda.org/microbiology2008.

Attention Given to Current Trends, Advances in Pre-Filled Syringes, Injection Devices

San Diego, Calif. • October 6–7 • www.pda.org/prefilled2008

Pre-filled Syringes Interest Group Leader Brigitte Reutter-Härle, Vetter Pharma-Fertigung and The Universe of Pre-filled Syringes and Injection Devices Program Planning Committee Co-Chair Shawn Kinney, PhD, Hyaluron

The market for pre-filled syringes is growing and will continue to develop very positively in the future. While the prospects are good, future success must not be taken for granted. The crucial criteria for growing demand are continuous improvements with respect to quality, safety, compliance, user-friendliness, cost-effectiveness and dosage precision. On October 6–7, *The Universe of Pre-filled Syringes and Injection Devices* will devote its attention to the current trends and advances in these systems.

Over the past few years, this event has evolved into the largest and most important international forum for sharing information on innovations and developments in the area of pre-filled syringes and injection devices. In the current program, the expert meeting will be addressing the industry's leading challenges and opportunities. Parallel sessions will be held to enable a larger spectrum of themes and presentations. This will allow participants to compile an individual program based on their own particular focus and interests.

Over the past few years, this event has evolved into the largest and most important international forum…in the area of pre-filled syringes and injection devices.

A fascinating aspect of this year's event will be the inclusion of the end-user perspective in product development and marketing. For the first time, the PDA conference will be spotlighting the needs of patients and health personnel when it comes to pre-filled syringes and injection devices. In the opening plenary session, Olympic swimming champion **Gary Hall Jr.,** who suffers from diabetes, will be offering insights into his experience administering his own insulin and use of injection devices. There will also be a lecture on how manufacturers and suppliers can learn from end-users and how and when end-user research can be planned and integrated in the development of new systems. The fact is, analysis of patient needs can quickly put development work onto a promising path. Usability is not merely a question of safety, but also a core aspect of customer satisfaction. Besides, this provides possibilities for identifying innovations and measures that can be applied to product lifecycle management.

Over the past few years, official regulations concerning pre-filled syringes and injection devices have become more stringent. This is an ongoing trend. That is why many of the lectures will be examining the best possible solutions and approaches that companies can adopt to deal with growing demands. A representative from the FDA will discuss current regulatory requirements already occurring during the opening plenary session. A case study will cover regulatory and quality issues in connection with the transfer of active substances from a vial to a pre-filled syringe.

A number of presentations will be focusing on quality issues when it comes to components and suppliers. Participants will be presented with the vital criteria that apply to the choice of materials, especially if components are acquired from different suppliers. The aim is to elucidate the impact of multiple-source components on suitability, efficiency and qualification strategies. Focus will also be on the influence of additional components resulting from the deployment of auto-injectors, which is, in turn, a

continued on next page

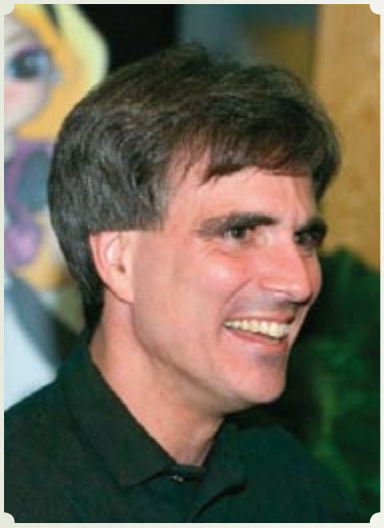
Networking Opportunities

In addition to the parallel sessions, the plenary sessions and poster presentation, this year's PDA event will provide networking opportunities for all interested group members on both days of the conference.

- On October 6, a lunch session will be used for various presentations on the trends in coating, such as siliconization and alternative means of lubrication.
- The day after, issues concerning safety devices will be discussed at a breakfast session.
- Because the number of participants is limited at these two events, please register early on for them. The networking event on the evening of October 6 and the breaks between the meetings will offer a great deal of opportunity for lively exchanges amongst participants about the items on the program.

2008 Annual Meeting Program Chair Honors Memory of Randy Pausch

Dear Friends and Colleagues,



We are mourning the loss of Prof. Randy Pausch, PhD, a keynote speaker during our recent Annual Meeting. He brought inspiration to many millions of people for his courage and positive outlook when faced with terminal pancreatic cancer.

Randy became known and loved by many people, when his "Last Lecture" held at his former University, Carnegie Mellon, was published on the Internet and viewed by millions of people globally.

His "Last Lecture," given by him for his children, had a tremendous effect on everyone of us, in some cases life-changing. His optimism and high spirits were exceptional. He has strengthened our resolve to find new treatments and cures for people like him.

He will be missed by all of us. Our sympathy and thoughts are with his family. Thank you Randy.

Maik W. Jornitz, PDA Chair-elect

Looking for the PDA Calendar of Events?

Go to www.pda.org/calendar for the complete listing of PDA conferences, workshops, TRI courses and chapter functions. Search capabilities allow for segmenting the listing by event type, place, month, year and/or keyword.

Also, a convenient hardcopy calendar of events for easy reference is provided with the January, April, July/August and October issues of the Letter.

Attention Given to Current Trends, Advances in Pre-Filled Syringes, Injection Devices,* *continued from previous page

resulting from the deployment of auto-injectors, which is, in turn, a product of the growth in the homecare sector. Discussions should be revolving around how manufacturers will be managing the subsequent increase in complexity. The requirements of new biotechnological substances, such as monoclonal antibodies, will also be explored. The lectures will highlight possible solutions for these special challenges.

Today, glass is the main component in the manufacturing of pre-filled syringes. It is extremely suited to these systems for many reasons, albeit it does need considerable care in production. One major topic at this year's PDA meeting will, therefore, be the proper handling of this material in aseptic filling. Among the lectures, there will be one touching on the possible difficulties caused by breakage and defects. It will look at how pre-filled syringes are produced and what types of defects can occur during manufacturing processes and handling. Furthermore, it will review methods which can be implemented in order to identify potential defects in glass syringes through optoelectronic detection.

The Universe of Pre-filled Syringes and Injection Devices offers an excellent opportunity to meet and talk with colleagues and specialists who work with all aspects of pre-filled syringes and injection devices. This year, an even greater number of participants is expected. The event is the largest and most significant forum on the topic, thanks to the presence of representatives of drug manufacturers, CMOs, suppliers, as well as experts from regulatory agencies.

We once again invite you to attend this unique event, which will be held October 6–7, at the Manchester Grand Hyatt San Diego Hotel in San Diego, Calif. We look forward to seeing you there.

PDA Conference on the Development and Regulation of Clinical Trial Supplies

November 10-11, 2008 • Boston, Massachusetts

Come together with international regulatory and industry representatives at the *PDA Conference on the Development and Regulation of Clinical Trial Supplies* to learn about the challenges and opportunities facing organizations involved in the manufacture, packaging, release and shipment of materials to clinical trial sites. Industry leaders will share expertise on topics from proof of concept to marketing authorization, and discuss lessons learned from actual case studies. In addition, FDA and EMEA representatives will provide an overview of the regulatory guidance for new medicinal product submission in the United States and Europe.

www.pda.org/clinicaltrials

A Look Back at Our First Year in Bethesda

Stephanie Ko, PDA

TRI TALK

It's a special month for TRI as we celebrate the one-year anniversary of the facility's completion in Bethesda, Md.! It's hard to believe that a year has passed so quickly when we still talk about the construction of TRI, like **Gail Sherman's** swing with a sledgehammer against a wall that broke nothing—because she hit a stud. **[Editor's Note:** The initial story of PDA TRI's demolition is in the April 2007 issue of the *PDA Letter* on page 46.**]** As we reflect on the events of the last year, we can be proud of our various successes and look forward to the many opportunities that will lead to bigger things to come.

Since its dedication in September 26, 2007, the TRI facility hosted, among other things, 26 laboratory and 5 lecture courses. New courses on topics like pre-filled syringes, fermentation and water microbiology demonstrated the training capabilities of the TRI facility to new and returning groups of professionals. Existing lab courses proved their enduring value when registrations sold out in five Aseptic Processing Training Programs, as well as the following courses:

- Environmental Monitoring Database & Trending Technologies
- Validating a Steam Sterilizer
- Advanced Environmental Mycology Identification
- Cleaning Validation

TRI seized one of its first claims to success almost immediately following its dedication when 40 officials from the Kazakhstan Ministry of Health attended three weeks of GMP-based training from November 27 to December 14, 2007. **[Editor's Note:** See the February issue of the *PDA Letter* on page 49.**]**

This great undertaking involved the delicate coordination of 16 instructors from all across the United States and Europe to provide expert regulatory and scientific training…all in Russian. This training was the first "full-scale" use of TRI's new lecture classroom, requiring us to utilize all of its audio/visual capabilities at once—a test that "validated" our careful design.

In addition to our training success, TRI paved the way for new opportunities in expanding the awareness of our tremendous potential. PDA produced a video highlighting the merit and distinction of the new state-of-the-art facility, including testimonials from senior leaders in the industry and the U.S. FDA. The video has been widely distributed, and can also be viewed on the TRI site at www.pdatraining.org.

Prospective students can benefit too—the TRI DVD provides ample justification for employers to feel confident in sending their employees here for training. Just send us a request for a DVD and you may benefit with a valuable training opportunity in return.

Another opportunity in uncovering TRI's potential was the ultimate facelift of our webpage, which was customized solely to incorporate sectioned viewings of our DVD, photos of the new facility, testimonials from credible sources, a FAQ page for prospective students and proper recognition of our generous sponsors. Check it out at the TRI site on the PDA website!

Our first year's accomplishments are only the beginning as we come to realize the facility's greater capacity for providing world renowned training. For example, utilization of the laboratories will be at its fullest yet, with 31 courses on the 2009 calendar in comparison to the 23 lab courses scheduled in 2008. Eight new and exciting laboratory courses will be introduced, including:

- Advanced Aseptic Processing
- CIP Design and Engineering
- Risk Assessment of Airborne Contamination–
  Safety Ventilation in the Biotech and Pharmaceutical Cleanroom

We look back at our first year in Bethesda with pride in our accomplishments and we look forward to new opportunities and experiences in the years to come. We extend our gratitude to all those involved in its success—our faculty, sponsors, students and supporters. As much as I've given credit to all that is new, I do believe that TRI's accomplishments are due to a calculated formula of applying past successes to new situations. The combination yields excellent opportunities for the people we serve for years to come.

Open, Detailed Discussions at Annex 1 Forum

Georg Roessling, PDA

PDA and the Asociación Española de Farmacéuticos de la Industria (AEFI) organized a discussion forum on the revised EU GMP Annex 1 on June 9 in Madrid, Spain. The discussion forum was attended by more than 130 participants including 25 inspectors from Spain. **Santiago Alsina,** President, AEFI, and **Georg Roessling,** Sr. VP, PDA, opened the forum and welcomed the participants.

The forum started with presentations about the regulatory and industrial perspectives of Annex 1. **Paul Hargreaves,** Principal Medicines Inspector, MHRA and the EMEA`s rapporteur on Annex 1 started the presentations. He gave insights into the creation of the document and highlighted the most relevant topics.

Christina Gómez-Chacón Galán, Chief Inspector from the Spanish authority AEMPS, and her colleague **Matilde Moreno García,** Inspector, described in more detail the impact of Annex 1 on manufacturing and gave examples for implementation. The last presentation given by **Roser Barnés Pallerols,** Validation - Aseptic Processing, Boehringer Ingelheim, gave an industrial perspective which highlighted some of the challenges companies face when implementing new requirements.

The presentations were followed by more than three hours of interactive discussions between regulators and industry representatives on the specifics of Annex 1. About 60 questions on media fills, capping, monitoring, and so forth were discussed. PDA will publish the questions and answers in the near future.

It appeared that all participants appreciated the open and, in some cases, very detailed discussion. By the end of the meeting, common understanding had been reached on many of the Annex's stipulations—an excellent way to begin putting this guidance into practice.

Ignacio Vilá, Industrial Director, Reig Jofré Group, thanked the people who organized everything so well (**Emma Fernández**, AEFI, **Mercè Pujol i Ameneiro,** Reig Jofré Group, and **Astrid Guenther,** PDA) and all participants before closing the discussion forum.

PDA and AEFI plan to keep the dialogue going at a future event now under development. Keep an eye on the *PDA Letter* "Europe" section for more details.

(l-r back row) Mercè Pujol i Ameneiro, Reig Jofré Group; Roser Barnés Pallerols, Boehringer Ingelheim; Santiago Alsina, AEFI; Georg Roessling,PDA; Ignacio Vilá, Reig Jofré Group, (l-r front row) Enrique Jó Cardoso, Reig Jofré Group; Matilde Moreno García, AEMPS; Christina Gómez-Chacón Galán, AEMPS; Paul Hargreaves, MHRA

PDA Conference to Dissect QbD: Part II

PDA Conference on QbD • Frankfurt, Germany • October 7–8

Mohammed Barkat, Batrox and Volker Eck, PhD, PDA

[Editor's Note: This is the second part of a two-part series on QbD and the upcoming PDA conference. In Part I, the authors discussed design space, citing a recent publication by Steven Nail and Jim Searles (*PDA Letter*, June 2008, p. 53. In Part II, the authors continue discussing Nail and Searles.**]**

Process analytical technology (PAT) is an integral part of QbD, because the paradigm relies on the use of an effective control strategy. PAT will be addressed in several case studies at the upcoming *PDA Conference on QbD: Practical Applications in Development and Manufacturing of Pharmaceutical Products.*

Nail and Searles[1] cite tunable diode laser absorption spectroscopy as a potential analytical methodology.

As experts in the field might know, a paper published by Chang and Fischer in 1995includes a graph that suggests an approach to establishing a design space for a freeze-dry process.[2] It illustrates the functional relationships among sublimation rate, product temperature and the two independently controlled variables in the process: shelf heat-transfer fluid inlet temperature and chamber pressure.

Regarding the first element of our design space variables, sublimation rate is discussed. The dilemma here, as the authors describe, is that within the range of chamber pressures used for pharmaceuticals and vaccines, the net effect of a higher chamber pressure is to increase the product temperature and sublimation rate of the product. This occurs because the improved heat transfer provided by higher pressure outweighs the negative effect on the sublimation rate of decreasing the driving force for flow of water vapor from the product to the chamber. As stressed by the authors, this sublimation rate should be determined experimentally to create the best possible cycle. Therefore, for the most efficient processing, it is desirable to operate at the highest possible shelf temperature and the lowest chamber pressure that still maintains the target product temperature during primary drying.

As stressed by the authors, this sublimation rate should be determined experimentally to create the best possible cycle.

The next step is to understand the other two elements of our design space: shelf temperature and chamber pressure. As discussed by Nail and Searles in creating a QbD approach, the development scientist must gain a superior understanding of a larger map of process conditions that produce an acceptable product. This understanding requires preparing trial batches under increasingly aggressive conditions until the product is unacceptable following a design-of-experiment approach that will unlock multivariable interdependences. Most commonly, the product will fail because of collapse. The collapsed material is characterized by a pharmaceutically unacceptable appearance, high residual water content and poor reconstitution characteristics.

For the sake of completeness, it has to be said that for predominantly crystalline formulations, the upper product temperature limit during primary drying is the eutectic melting temperature. Exceeding this melting point during primary drying causes puffing of the vial contents, accompanied by a loss of pharmaceutical acceptability. The upper product temperature limit during primary drying should be determined during characterization of formulations intended for freeze-drying, using low temperature thermal analysis, freeze-dry microscopy, or both.

In our hypothetical exercise to identify design space elements, it is essential to understand the limitations of the performance of laboratory-scale, pilot-scale, and production-scale freeze-drying equipment and its impact on refrigeration capacity, condenser capability, heating capacity, or limitations of the dynamics of water vapor flow within the system.

Program Planning Committee

Mohammed Barkat, Co-Chair of Conference, formerly Draxis, Canada

Michiel Rook, Co-Chair of Conference, Millipore, France

Mette Bryder, Lundbeck, Denmark,

Paul Dickinson, AstraZeneca, UK

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Lynn Torbeck, Torbeck & Associates, USA

As the authors point out, equipment limitations can take many forms. For example, the condenser has a limit as to the flow rate of water vapor that can be condensed while keeping the surface temperature of the condenser adequately low. The heat-transfer system supplying the heat of sublimation of ice is limited in the amount of heat that can be transferred in a given period of time.

Equipment limitations of this type take the form of a maximum sublimation rate that can be supported by the equipment irrespective of the pressure in the system, and they therefore appear as an upper boundary on the design space.

There is another, more complicated limitation on the performance of freeze-dryers discussed by the authors, which has to do with the dynamics of vapor flow in the duct that connects the chamber to the condenser.[3] Vapor flows through this duct because of the difference in water vapor pressure between the chamber and the condenser. Thermodynamic theory shows there is a limit to this velocity corresponding to the speed of sound in water vapor—about 400 meters per second, or Mach 1. The speed of sound does not change with pressure. As the velocity of water vapor approaches Mach 1, the flow of water vapor is choked, and further reduction in the downstream pressure has no influence on the mass flow rate through the duct. In freeze-drying, choked flow is characterized by loss of control of pressure in the chamber. Thus, for the sake of this example, the design space is bounded by the upper product temperature isotherm and by the choke. Any process conditions in the design space would be acceptable. Of course, it is most desirable to operate near the most efficient process conditions.

As shown by this example, it is important to view product and process development for freeze-dried parenterals as an integrated process rather than as a collection of independent activities. To generate a design space similar to the one described here, it is necessary to have a thorough understanding of both the characteristics of the formulation and the capability of equipment.

We look forward seeing you in Frankfurt.

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