Science • Technology • Quality • Regulatory • Community

PDA Letter

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September 2007

In This Issue…

PDA Parenteral Drug Association

Connecting People, Science and Regulation®

Method Validation: An Overview of Global Standards

Susan Schniepp, Mae Taylor, Dave Loffredo and John Vasinko, Hospira, Inc.

Regulatory agencies, compendial authorities and independent organizations routinely publish information about method validation requirements. This article identifies and discusses validation guidance issued by various organizations including The International Conference on Harmonisation (ICH), the European Pharmacopœia (Ph. Eur.), the United States Pharmacopeia–National Formulary (USP–NF) and the Japanese Pharmacopœia (JP).

There are four distinct categories of methods: chemical, physical, biological and biotechnological. Chemical and physical methods are the most common tests used today for drug substance, excipients and drug product analysis. Typical chemical methods include chromatography (high-pressure liquid, gas and thin-layer) and traditional wet chemical analyses for identification. Physical methods include loss on drying, residue on ignition, pH and other technique-dependent methodologies. Biological methods include traditional tests for determining microbial contamination such as bacterial isolation and enumeration, bacterial endotoxins, microbial limits, sterility and specific organism identifications. Biotechnological methods are becoming more common as this field continues to grow. Methods in this category include protein and peptide analysis (e.g., isoelectric focusing, ELISA, Western Blot, etc.). *Table 1* illustrates the four method categories and the organizations that publish guidance on validation consideration. Each of these method categories employs different validation concepts in determining the applicability of the method to the product(s) being analyzed.

Table 1: Summary of Method Type and Validation Information Source

Method Type/ Reference	Chemical	Biological	Biotechnological	Physical
ICH	Yes	Yes	Yes	No
USP-NF	Yes	Yes	Yes	Yes
Ph. Eur.	No	Yes	Yes	Yes
JP	Yes	Yes	Yes	Yes
ASTM	No	No	No	Yes

continued on page 20

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The PDA Annual Meeting is the one meeting each year dedicated to advancing the careers of pharmaceutical and biopharmaceutical professionals by focusing program content on science and technology innovation, offering extensive formal and informal networking opportunities and providing a forum to contribute to and influence the advancement of science and regulation in the industry.

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Visit us at the 2nd Annual Global Conference on Pharmaceutical Microbiology, October 29–30, 2007 — Table 10

Table of Contents

Cover art:
This issue's feature story provides a comprehensive examination of compendial standards for analytical method validation.

Coming Next Month
Next month's issue will contain a comprehensive report from PDA's May workshop on QbD. To advertise, contact Cindy Tabb at +1 (301) 656-5900, ext. 222 or tabb@pda.org.

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Dublin, Ireland

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Shanghai, China

Editor's Message

Those readers who follow the *PDA Letter* editorial calendar might notice that this issue's feature article does not cover computer validation, as promised on the table of contents page in the July/August issue. But, as any process reliant on outsourced raw materials, there can exist variability and supply bottlenecks. In this case, the article we were to publish on computer validation was not quite ready for this issue, while the feature article for the October issue on global pharmacopeial standards for analytical method validation was in hand and publishable. Therefore, we made a last minute decision to make the switch. We apologize to those expecting articles on computer validation, and we thank our authors from Hospira Inc. for their strong effort on this month's cover story. We hope readers will let us know if they find this month's feature article—or any article in this issue—valuable and informative. Contact me at morris@pda.org with comments, suggestions and/or complaints.

PDA is introducing an additional member benefit this month, *International Pharmaceutical Quality*—a new publication from the former editor of *"The Gold Sheet"*, **Bill Paulson.** PDA's **Jim Lyda** sat down with Bill to discuss his new product (see page 8). Jim also met with ZLG's **Sabine Paris** to discuss this relatively new German authority's roles and responsibilities; this informative discussion begins on page 32.

Also in this issue, we are launching the Quality & Regulatory Snapshot to help members better track PDA's activities in this area.

In addition, we have introduced a new section to the Letter for Europe to help members keep track of PDA events and other developments there.

The Membership Resources section includes a new feature—the Volunteer Spotlight, which focuses this time on PDA Chair-Elect **John Shabushnig** (page 38). Accompanying John's Spotlight is an interview with John about the recently established Membership Committee.

Gail Sherman is back with her first report from the new TRI facility (page 48).

Visit www.pda.org/pdaletter

At the Letter's new website, you can read selected articles and link to the members-only archive *before* your hard copy arrives in the mail! Also, you can easily submit your comments and have them published as "Letters to the Editor." Click on the "Authors Wanted" link to learn about upcoming topics and how to submit articles!

The PDA Letter is published 10 times per year, exclusively for PDA members. Subscriptions are not available. Articles in the PDA Letter may be reproduced with permission—contact the PDA Letter Editor for details.

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Bill Paulson's IPQ: Newest Member Benefit

PDA's Lyda Talks with Paulson on New Pub

Starting in September, PDA members can look forward to an additional member benefit resulting from a collaboration between the Association and **Bill Paulson,** formerly of *"The Gold Sheet",* which will create a new industry publication entitled *International Pharmaceutical Quality* (IPQ). Paulson will be Editor-in-Chief of the new bimonthly periodical.

Paulson will provide independent, unbiased journalism of key international quality initiatives and harmonization efforts involving industry associations, global regulatory agencies, pharmacopeias and standard-setting organizations. As a key players in the evolving regulatory model and the harmonization effort, the U.S. FDA, the EU's EMEA and other regulatory agencies worldwide will be important targets of IPQ's coverage.

IPQ will directly target the relevant issues surrounding international harmonization and help further the discussion about the regulatory approaches appropriate for advancing products and processes. Each issue will provide an in-depth analysis of a problem area in the forefront of the regulatory debate, with a focus on the efforts to improve and harmonize the regulation of pharmaceutical quality, as well as internal corporate quality systems.

"*International Pharmaceutical Quality* will be included as a valuable new benefit in the PDA membership package," said Robert Myers, PDA President. "We hope to partner with other associations to offer this important new publication to their members as well."

Lyda: I would like to congratulate you on the launch of your new publication. Can you explain what IPQ is all about?

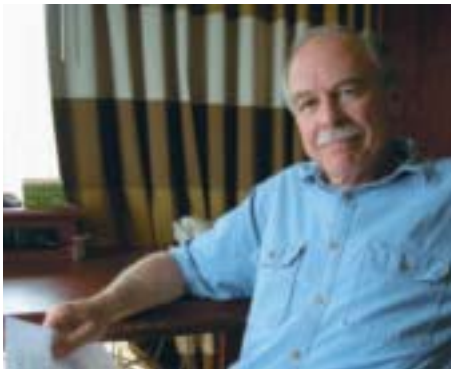
Paulson: The goal of the publication is to delve into and help move forward the ongoing global dialogue between industry and regulators about creating a new paradigm for regulating drug and biotech product quality. It is challenging to everyone to find mechanisms to come together and solve regulatory problems outside of their own borders. IPQ will focus on that challenge and the efforts to address it.

Lyda: How do you see IPQ contributing to this process?

Paulson: I see *International Pharmaceutical Quality* as really getting inside of the effort to think globally and evolve the regulatory paradigm on an international level. We are in a situation right now for FDA and for the international pharmaceutical industry where local or regional solutions to the problems that exist in creating a more flexible and technologically friendly regulatory environment are stymied by the limitations of disharmony once those borders are crossed. So the problems are forcing the pharmaceutical community to look for solutions on an international level. IPQ is squarely centered on what those problems are, what the challenges are, what the hurdles are and how industry and regulators are working together to try and solve those problems.

Lyda: You are well-known as the former editor and lead author of *"The Gold Sheet"*, which has been something of a standard for quality and compliance information in our industry. How long were you involved with that publication?

Paulson: Over two decades. My involvement with *"The Gold Sheet"* came at a pivotal time in pharmaceutical regulation, right after the Waxman/Hatch legislation was passed back in 1984—really the genesis of the current generic industry in this country. The legislation forced FDA to come to grips with and try to standardize its chemistry, manufacturing and controls (CMC) policies around what it wanted to see in drug applications. Those quality issues were at the very heart of whether the generic applications were going to pass muster at FDA, and it forced a real concentration on CMC standards that spread over into the NDA world and resulted in new CMC guidances and policy formulations for new drugs as well during the 1980s.



Bill Paulson

Also, the biotech community was developing at that point in time, so FDA was also having to wrestle with putting in place some meaningful guideposts on CMC in that technologically complex area.

Lyda: How do you describe this unique relationship with PDA?

Paulson: PDA is going to be an important helpmate to IPQ in providing administrative support for the publication. With its base in Bethesda, Md., and reach into the quality regulatory community worldwide, PDA is well-suited to provide the support that is needed to produce and help distribute the publication. Our goal is to provide IPQ to PDA members as part of their membership benefit package.

I will also be working with other organizations involved in the regulatory dialogue worldwide to track their dialogue and partner in the IPQ distribution process. So I very much look forward to continuing my close connection with a variety of groups and organizations globally.

Lyda: How will IPQ contribute?

Paulson: I think IPQ can help by educating people on where the dialogue is right now and who is coming up with potential solutions to further the movement towards harmonization. Also, IPQ can give readers the knowledge base to get more involved in shaping the regulatory approaches they will live with later.

Lyda: How are you going to do that?

Paulson: It is a question of having your ear to the sounding board. It is a question of following that dialogue—going to meetings and forums that are at the forefront of those discussions. It is a rapidly changing regulatory world. The information challenges are immediate and real—keeping your eyes on those that are the drivers for that process.

It is tracking where the forums are that are likely to be most productive and where industry is meeting directly with regulators, and then listening carefully to what the issues are and who the drivers are and where the good ideas are coming from—talking to the key players and analyzing the efforts to formalize regulations, guidance and standards and the comments and discussion around those efforts.

Science & Technology *Snapshot*

Microbiology – A PDA Core Competency

Rich Levy, PhD, PDA

As an environmental microbiologist, I had many choices of associations to join when I began my career. My main membership was the American Society for Microbiology, and the primary Journal I read was *Applied and Environmental Microbiology.* I quickly learned that this was not enough to sustain a career directed toward the pharmaceutical and biotech industries, and that I needed to read relevant publications and network with those who were active in this area. I found that PDA members were asking and answering many of the questions I had on subjects such as the microbiology of activated carbon columns and high purity water systems, bibful formation, environmental control in manufacturing environments, sterile filtration and viral clearance. So I joined PDA.

Early on, by attending PDA meetings and reading the *PDA Letter* and the Journal, I was introduced to many long-time PDA members such as **Doris Conrad, Mike Korczynski, Jim Akers, Jim Agalloco** and **Klaus Haberer** to name a few, who were very interested in addressing the microbiological challenges facing our industry in aseptic processing. I had also met PDA members who were interested in rapid microbial identification and detection, like **Jeanne Moldenhauer** and **Michael Miller.** This in turn led to other valuable interactions, including many with FDA staff who shared similar interests.

In recent years, however, PDA seemed to focus less and less on microbiological sciences and more on regulatory and quality issues. Although I share this interest too, I thought it was unfortunate that PDA limited its support of microbiology to presentations at Interest Group meetings, the Annual Meeting and TRI courses. Where could you go to hear the latest and greatest on new technologies and best practices in microbiology? Then, USP stopped holding its microbiology meeting, and I saw an opportunity

continued on page 13

Technical Report *Watch*

In Global Review: *Drafts of the following TRs are under review by the global PDA membership. To learn how to comment on any one of the drafts, contact Genevieve Lovitt-Wood at glovitt@mindspring.com.*

- **TR-15 (Revised 2007),** ***Validation of Tangential Flow Filtration in a Biopharmaceutical Application***
- ***Reprocessing of Biopharmaceuticals***

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

- ***Aseptic Processing Risk Management***
- **TR-14 (Revised 2007),** ***Validation of Column-Based Separation Processes***

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.

- ***Biological Indicators for Sporicidal Gassing Processes: Specification, Manufacture, Control and Use***
- **TR-26 (Revised 2007),** ***Sterilizing Filtration of Liquids***
- ***Filtration of Liquids Using Cellulose-Based Depth Filters***

In Production: *Once approval is achieved, each TR is formatted, printed and sent to members, typically packaged with the PDA Journal.*

- **TR-43,** ***Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing***

Advisory Board *Watch*

PDA's Audit Guidance Advisory Board Update

Janis Olson, EduQuest

PDA established the Audit Guidance Advisory Board (AGAB) to periodically review and approve changes to the process model and data collection tools described in PDA Technical Report No. 32, *Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations.* The AGAB also monitors auditor qualification and re-qualification requirements and provides oversight of the SynTegra Audit Resource Center (ARC) to ensure the process remains current with respect to changing technology and regulatory environments; to periodically analyze ARC's registration history, promotional efforts and service performance; and to furnish ARC with suggestions, if any, for improvement.

The objective is to maintain an audit process that meets the requirements for consistency and reliability in execution, while facilitating the sharing of results through the Audit Process Model and Data Collection Tool. This ensures that the audit information, presented as an audit report, is usable in supporting procurement activities and in inferring structural integrity of supplier

continued on page 13

Leadership *Opportunities*

If you are interested in integrating your time and skills in the below projects, please contact **Iris D. Rice,** Executive Coordinator, Scientific and Regulatory Affairs, PDA, at rice@pda.org. Please be prepared to offer a short biographical sketch outlining your areas of expertise and interest pertinent to the development of this project. We encourage you to offer your time, skills and expertise to this project and appreciate your participation!

Analytical Method Validation for Biotechnology Products Task Force

The new Analytical Method Validation for Biotechnology Products Task Force, chaired by **Nadine Ritter,** PhD, Biologics Consulting Group, and **Gautam Maitra,** Head of Regulatory Affairs, AC Immune, Switzerland, seeks biotechnology product analytical test method experts to actively participate in the implementation of a technical report. The emphasis

continued on page 13

Task Force *Corner*

The following Task Forces are gathering at the 2007 PDA/FDA Joint Regulatory Conference.

Appropriate Application of GMPs for Phase I/ Phase II Clinical Bioprocess API

The task force began its work with a kick-off meeting to discuss the scope of the project, the deliverables and the target completion date for the project. The task force will complete a technical report detailing the individual aspects of GMP requirements that apply to the manufacturing of Phase I and Phase II clinical materials. The task force will meet at the upcoming 2007 PDA/FDA Joint Regulatory Conference.

Analytical Method Validation for Biotech Products

The Analytical Method Validation for Biotech Products Task Force will have a kick-off meeting during the 2007 PDA/FDA Joint Regulatory Conference on Sunday, September 23 at 6:00 p.m. This meeting will initiate the development of a technical report to address the components of adequate and appropriate test method development and documentation for biotech products.

Technical Report No. 22 Task Force: *Process Simulation Testing for Aseptically Filled Products*

The task force will meet during the 2007 PDA/FDA Joint Regulatory Conference and also at PDA's headquarters in Bethesda, Md., in October to finalize the upcoming technical report rewrite.

Virus Filter Task Force

The Virus Filter Task Force will meet at the 2007 PDA/FDA Joint Regulatory Conference on September 27 to continue their project on the *Nomenclature for Small Virus Filtration* technical report. Subsequently, and in connection with the Virus Filter Task Force, the Virus Spike Preparation Standardization Task Force, under the direction of **Hannelore Willkommen,** PhD, RBS Consulting, and **Martin Wisher,** PhD, co-chair, BioReliance Invitrogen Bioservices, will meet on September 27 to continue the work on the deliverables of their upcoming technical report and to review the recent results of a survey to determine current thinking, client needs and CTO feasibilities concerning virus spike preparations.

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For more information visit:

www.pda.org/europe

or please contact: info-europe@pda.org

Microbiology - A PDA Core Competency, continued from page 10

to revive PDA's role in driving the microbiological sciences by creating a partnership with USP.

The result was our 1st Annual Global Conference on Pharmaceutical Microbiology, which was held last October in Bethesda, Md.

As October approaches, we are looking forward to PDA's second annual microbiology meeting. More than two hundred and fifty attendees and exhibitors attended last year's inaugural meeting, and we are expecting even more this year. Last year's USP session was a hit with the attendees, and this year we are expanding our agenda to include European and Japanese pharmacopeial representation. We have a speaker from the TGA, Australia's regulatory agency, making this meeting truly global. This meeting now complements our very successful Global PDA/EMEA/FDA Viral Safety Meeting and our new focused meetings on rapid microbiology and mycoplasmal contamination of biotech products, which are held at both the regional and international levels.

When combined with our emphasis on microbiology courses at TRI, PDA is again offering additional member and industry value by creating deliverables we all can use to improve the quality of pharmaceuticals.

Advisory Board Watch, continued from page 11

products and services used in the pharmaceutical, biotech and medical device industries.

The AGAB has a strategic mission to review the auditing needs of the industry and expand the auditing process model to other areas.

Currently, the AGAB has ten voting members and one vacancy. The members are: Virginia Corbin, Water Corporation; C. Wells Horton, Procter & Gamble; Peter Miller, Bristol-Myers Squibb; Winnie Cappucci, Bayer Healthcare; Elien Young, Novartis Pharmaceuticals; Charles Steiniger, Sparta Systems; Phil Lofty, Pharmaceutical Services Corporation; Tom Rudzinski, Software Reliability and Statistical Services; Catherine Luk, 3M; and Janis Olson, EduQuest.

Others who attend the meetings include: Tom Menighan and Debbie King, SynTegra; Charlie Waite, Process Design Consultants; and PDA's Rich Levy, PhD, and Gail Sherman.

AGAB has had six teleconferences and one face-to-face meeting at PDA's headquarters. During the meetings, the group reviewed the activities of the Audits Resource Center; worked on revising its charter and procedures; and determined that the Technical Report No. 32 model should be used to conduct other types of audit. These additional audit facilities include web and application service provider hosting facilities, clinical research organizations, electronic data capture hosting, call centers and data repositories, as well as other supplier organizations to the pharmaceutical industry.

In 2007, the AGAB supports the formation of a PDA task force to expand the Technical Report No. 32 model to other audit areas. The mission statement and the charter for the task force have been presented to the PDA Board of Directors.

Leadership Opportunities, continued from page 11

will be on method prequalification work, method specificity, and method robustness. Examples used in the technical report could include gel electrophoresis, size exclusion chromatography and immunoassay methods. Task force leaders are seeking EU and U.S. representation as the task force develops to address the components of adequate and appropriate test method development and documentation for biotech products.

Development of VHP Contamination Task Force

PDA is seeking a task force leader, co-chair and volunteers to participate in an upcoming task force on the *Development of VHP Contamination*. The expected deliverable is a PDA technical report addressing the development of decontamination cycles for isolators used in the manufacturing and testing of pharmaceutical products. PDA is seeking volunteers with expertise and interest in decontamination, isolator design, cycle development, instrumentation, BI selection, and validation/qualification strategies and acceptance criteria.

Recent Sci-Tech Discussions: Software Validation and Reusability of Single-Use Technology

The following unedited remarks are taken from PDA's Pharmaceutical Sci-Tech Discussion Group, an online forum for exchanging practical, and sometimes theoretical, ideas within the context of some of the most challenging issues confronting the pharmaceutical industry. The responses in the Sci-Tech Discussions do not represent the official views of PDA, PDA's Board of Directors or PDA members. Join at www.pharmweb.net/pwmirror/pwq/pharmwebq2.html.

Software Validation

I request your valuable inputs regarding exact requirements for the validation of QC lab instruments software.

Systems like HPLC, GC are standard models available in market [and are] provided with software for all kinds of analysis, data recording, etc. These are licensed [and] certified software.

[Does this] software require validation? What kind of validation is to be done? My QC colleague is suggesting that there are standard packages [and] do not require validation?

Respondent 1: Software [for] Chromatography Data System (CDS) requires validation. Software reloads or upgrades are considered major repairs, but for data systems this may not require a PQ. Important criteria for qualification of proper software functionality include verification of the revision and the correct files associated with that revision, proper computational capability and system control functionality.

An IQ should be performed whenever loading new software, reloading software (such as after a hard drive failure), adding service packs to the operating system, or upgrading software to verify that the proper files are present. An OQ should then be performed to verify accuracy of the CDS's computational capability. System suitability should be the final step to verify proper system control functionality. If it is time to re-qualify the entire system, then a PQ should also be performed before system suitability, but this is not necessary to merely verify system control functionality. Adding service packs to CDS software can be major or minor depending on the specific changes they make. Always refer to the change notes and other appropriate documentation to determine what is affected. Minimally, an OQ and system suitability should be performed after software changes.

Respondent 2: Other than the usual, calibrate the instrument then validate. My usual answer here, for the purpose of defining a plan and learning the basics, is to point to a probably dated approach now of deciding on a Holistic Validation or a Modular Validation. For the details, I suggest getting a copy of: W. B. Furman, T.P. Layloff and R.F. Tetzlaff, JAOAC, 77 (5), 1314-18, 1994.

Respondent 3: Ask your colleague to read USP <1058> titled "Analytical Instrument Qualification." ISPE also has a GPG guide titled "Validation of Laboratory Computer Systems." It covers which instruments need to be qualified in what manner.

Even if you call it commercial off the shelf software (COTS), it requires qualification. At the minimum you should have a DQ/IQ/OQ/PQ. That is assuming you have a URS and FS in place before you decide to purchase the instrument.

Reusability of Single-Use Technology

I am investigating the possibility of extending the use of disposable bags by refilling the bag in a sterile/aseptic manner. The bags are currently single-used disposables and used for either medium or harvest storage in a perfusion fermentation process. The proposal could be one of three options:

1. **Refill the medium bag with new medium (same type of medium only or even same lots only)**
2. **Refill the harvest bag with new harvest (same type of intermediate product only or even limited to the same fermenter)**
3. **Refill the medium bag with harvest, where medium is added to a continuous perfusion fermenter, and harvest from the fermenter is collected in one of the empty medium bags**

Other than the technical and regulatory aspects, I am particularly interested in the compliance restraints other than GMP and microbiological contamination.

Typical questions are related to:

1. **The impact on the expiration periods. What strategy can/should be used to allow for maximum flexibility?**
2. **The impact of medium (or harvest) residuals that are carried over to the next medium (or harvest) lot. Could there be a blending issue?**
3. **For option 3: Could there be an issue regarding carryover of unused medium components (not processed during fermentation) to the harvest, originating from the residuals in the reused emptied bag? Please note that we use a continuous fermentation process, where medium is continuously added, and harvest is continuously removed**

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Does anyone have experience with the extended use (reuse) of disposable bags or do you have any comment on the subject?

Respondent 1: Interesting question. Is this economic or scheduling driven? What is the vendor recommendation? I assume they sell these bags as single-use items. Can you make multiple aseptic connections without increasing the risk of microbial contamination? Do the media have a short expiry time? What is the economic cost of bag failure or contamination?

Respondent 2: I can't understand why you would want to reuse disposable bags, and, for a GMP or pharmaceutical development environment, I would not do that (I'm not a bag manufacturer).

I don't know your process or desired use, but here are my thoughts.

I have seen some research organizations reuse or recondition disposable bags for fermentation processes, where there is a medium component adsoption problem, in order to save money on the bags and their connections or where there are subsequent disposal issues. However, for me, the savings are outweighed by the inconveniences. These inconveniences would include practical and organizational issues such as cross contamination, how to easily and aseptically add new batches of medium or components to recycled bags, sterility (your chances of contamination will increase), also, the acceptability of the data generated from such use. Finally, some of these bags are not strong enough for repeated use.

Putting aside the GMP and regulatory issues regarding reuse, I do not honestly find the practice scientifically and technically acceptable:

- I would not mix the same or different lots of fresh medium repeatedly into the same disposable bag. For example, how would you trace a medium problem (defective or sterility) if you mix several lots in or via one bag and use that to feed your bioreactor process? You've got no traceability and could risk condemning the entire run (expensive).
- Same for the harvest, how do you know that successive harvests are the same or stable until you have proved that? To be scientifically and technically correct, you should keep them separate until appropriately tested or have shown that they are the same, before mixing.

The best approach would be to use disposable bags as intended, i.e., disposable, as you have been doing. For example, multiple disposable bags to be connected via a manifold with sterile connectors, for medium supply or harvests.

Respondent 3: I am intrigued why one would try to reuse disposable bags. If it is economics, it is a very risky path to walk; but, moreover, the cleaning cost of the bag would be way higher than a new bag. Disposable bags were invented due to the fact that cleaning costs are down and set-up times accumulate to a degree far higher than the cost of a disposable bag. A rough analysis showed that the cleaning of a 100 liter tank can cost from $5,000-10,000, depending on WFI and labor costs. A 100-liter disposable bag runs in the hundreds and not thousands. Besides, it is ready-to-use in minutes and not hours.

Moreover, disposable bags are prest-erilized by gamma irradiation. This irradiation process and the stability of the bag are validated. This validation exercise has to be performed again for any reuse. My gut feeling says that the leachable level will rise, as well as particulates. Shelf life will be reduced greatly and probably also mechanical stability. Having said this, the bag needs to be real clean to avoid any form of degradative contaminant due to gamma irradiated residues.

To summarize, it is truly not worth it.

Respondent 4: I cannot comment on the extended use of bioprocess bags in GMP manufacturing, but I have seen the strategy used quite successfully in non-GMP pilot plant perfusion culture. We maintained a continuous perfusion operation for a month, topping off a medium supply bag every few days and removing conditioned medium continuously to a harvest bag exactly as you describe. In our case, the motivation was not economic; it was a direct translation of a process from stainless steel tanks to disposable components, and operationally it would have been more difficult to use new bags than to reuse.

It seems to me that you have two separate issues. The first concerns the regulatory questions around dividing a continuous perfusion operation into batches. Questions about mixing batches of medium, mixing harvests and extended re-batching of vessels (without cleaning) are relevant regardless of whether you are using stainless steel vessels or bags.

The second issue is the reuse of bags. If you can configure your tubing sets such that you do not need to make and break connections within your sterile barrier, or you have validated methods for making new connections, I would not expect this to be a regulatory hurdle. Concerns about leachables should be mitigated by the fact that cell culture media are often stored in these bags for a year or more, and an assessment of leachables can be built into your process validation just as it would for a batch operation.

I am very interested to hear what others have to say on this topic.

Respondent 5: In November, there will be an event about this topic: www.bio-production.com.

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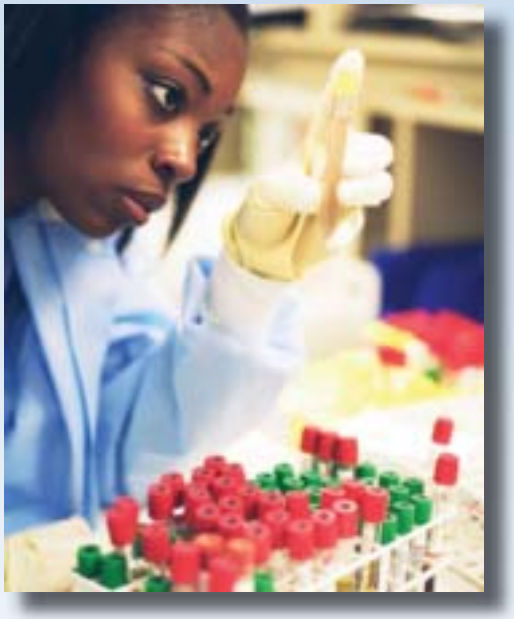

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Method Validation: An Overview of Global Standards, continued from cover

Each of the standard setting organizations in *Table 1* operates independently from each other in determining what is appropriate to publish.

ICH is a global organization (see Diagram 1) made up of regulatory and industry representatives. The guidances published by this organization are arrived at through consensus and are ultimately adopted by the regulatory authorities in the United States, Japan and the European Union. The European and Japanese Pharmacopœias are connected with the governments in their respective geographical locations. This association to ICH allows the Ph. Eur. and the JP to adopt ICH guidance with little or no change. The USP–NF, on the other hand, is an independent standards-setting organization that operates by a majority vote of elected expert committee members from the medical, industrial, academic and regulatory disciplines. Because the USP–NF is independent, it has the ability to modify the ICH guidance before adopting their recommendations in its official publications.

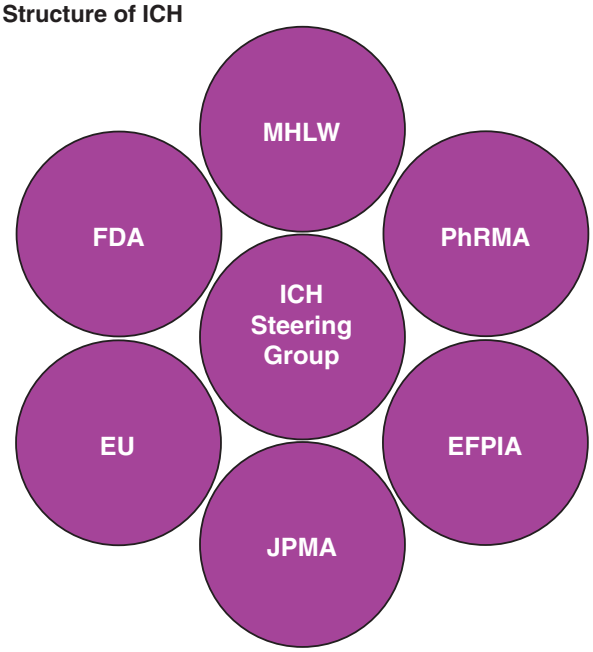
Chemical Methods

The majority of the traditional chemical methods are used to analyze small (low molecular weight) molecules which are usually synthetically derived. The reason for validating these methods is to demonstrate the suitability of the particular method chosen for its intended use. The most common types of chemical methods are identification, impurities-quantitation, impurities-limit and assay. A summary of the validation parameters applicable to these types of methods is shown in *Table 2* (next page). The notes underneath the table summarize additional points for consideration regarding different method types. The "+" indicates the typical parameters normally evaluated for the particular method type; the "–" means the specific parameter is not needed for method validation purposes.

Each method type listed in *Table 2* is used in characterizing the molecule being analyzed. Identification tests are intended to ensure the identity of an analyte in the sample preparation. Impurity tests can be either a quantitative test or a limit test and are used to identify and determine the level of suspected impurities in a given sample or product matrix. Assay tests are intended to measure the amount of analyte(s) present in a given sample, the presence of any preservative (if applicable), and the uniform distribution of the molecule in the product (content uniformity) as well as to determine the dissolution profile for a specific product batch. A stability indicating assay is a validated quantitative analytical procedure that accurately measures a property of the drug substance or the drug product without interference from impurities, degradation products, excipients or other components of the sample matrix.

System suitability tests are an integral part of test methods utilizing system-based instrumentation. System suitability testing is used to confirm the operating system is functioning correctly, independent of the environmental conditions, at the time of use. These tests are based on the concept that the equipment, electronics, operations and samples to be analyzed constitute an integral system that can be evaluated in its entirety. System suitability is required for instrumental chromatographic methods, but may be used for other test methods, as appropriate. Selection of system suitability tests and associated criteria shall be based on the type of test and intended use of the method. *Table 3* (page 22) indicates some of the available

Diagram 1: Structure of ICH



EU: European Commission-European Union
FDA: Food and Drug Administration, United States
MHLW: Ministry of Health, Labour and Welfare, Japan
PhRMA: Pharmaceutical Research and Manufacturers of America
JPMA: Japan Pharmaceutical Manufacturers Association
EFPIA: European Federation of Pharmaceutical Industries and Associations

Table 2: Validation Requirements vs. Method Type

Type of Method / Validation Parameter	Identification	Impurities: Quantitation	Impurities: Limit	Assay
Accuracy	—	+	— [3]	+
Precision:				
Repeatability	—	+	—	+
Intermediate Precision	—	+ [1]	—	+ [1]
Reproducibility	—	+	—	+ [1]
Specificity[2]	+	+	+	+ [6]
Detection Limit[4]	—	— [3]	+	—
Quantitation Limit[5]	—	+	—	—
Linearity[7]	—	+	—	+
Range	—	+	— [3]	+
Robustness	—	+	—	+

1. Intermediate precision or reproducibility should be performed. In cases where reproducibility has been performed intermediate precision is not needed. ICH defines intermediate precision as expressing "within-laboratories variations: different days, different analysts, different equipment, etc.
2. Lack of specificity of one test method could be compensated by other supporting test method(s).
3. May be needed in some cases (e.g., not required for potassium permanganate oxidizable substances test, or when a control standard is used to determine the pass/fail status of the sample by comparison of area count only, but is required for TOC determination organic impurities in water for injection.).
4. It is not always necessary to determine the absolute limit of detection.
5. It is not always necessary to determine the absolute limit of quantitation.
6. Lack of specificity for an assay for release may be compensated for by impurities testing.
7. ICH requires expression by correlation coefficient.

information sources for guidance of the validation of chemical methods.

Traditional Biological Methods

Validation of traditional biological methods operates under a different premise than that of chemical methods. Instead of determining the presence and identity of a chemical molecule, the user is asked to assure that bacteria and their by-products are absent from ingredients and final products. Methods in this category include isolation, enumeration, growth promotion, microbial limits, bacterial endotoxin detection, sterility, antimicrobial effectiveness and detection of various pathogenic bacteria (e.g., *Salmonella* species, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*). Validation of these methods focuses on the recovery of objectionable organisms.

Manufacturing processes may damage any bacteria potentially present in the API or excipients. In order to determine if bacteria were present and the level of the contamination, conditions conducive to bacteria growth must exist. Providing optimal growth conditions for bacterial recovery requires the analyst to neutralize interference from any product ingredients and to assure the material under test does not inhibit growth.

The validation continues with methodology to identify the bacteria if it is recovered. This identification requires the recovered bacteria to be compared with characterized known cultures. Identifications are accomplished by comparing metabolic, genotypic or phenotypic characteristics to those of known organisms. There are at least 521 culture collections maintained in 66 countries worldwide. The most predominant cultures used in compendial standards are those available from American Type Culture Collection (ATCC), National Collection of Type Cultures (NCTC), National Collections of Industrial Food and Marine Bacteria (NCIMB) and Collection de L'Institut Pasteur (CIP). These cultures are also used in growth promotion which assesses the ability of the media to support the growth of the bacteria, if present.

Traditional biological methods require a minimum of two days to determine the presence of bacteria. In the case of the sterility test, a total of 21 days maybe needed before the final result is known. Many companies are exploring the use of rapid microbiological methods to obtain results in a timelier manner. Recognizing the industry's need for real-time results, the Ph. Eur. and the USP-NF have started publishing information regarding the validation of rapid micro methods.

In addition to assessing the bacterial bioburden in APIs, excipients and final product, bacterial methods are also used to determine if there was any residual contamination from the lipopolysaccharides from gram negative bacterial cell walls. The most popular test for determining this residual contamination is by using one of the three types of bacterial endotoxin (BET) tests: gel clot, chromogenic or kinetic. Validation of BET methods requires the user to determine inhibition and enhancement properties of the material under test as well as other key parameters. Materials that are not able to be tested by BET methodology must be tested by the rabbit pyrogen test.

Table 4 (page 22) is a summary of some of the available information sources for guidance of the validation of

Table 3: Summary of Chemical Method Validation Sources

Parameter	ICH	USP	Ph. Eur.	JP	FDA[3]
Specificity	yes	yes	no	yes	yes
Accuracy	yes	yes	no	yes[1]	yes
Precision:					
Repeatability	yes	yes	no	yes[2]	yes
Precision:					
Intermediate precision	yes	yes	no	yes	yes
Precision:					
Reproducibility	yes	yes	no	yes	yes
Detection Limit	yes	yes	no	yes	yes
Quantitation Limit	yes	yes	no	yes	yes
Linearity	yes	yes	no	yes	yes
Range	yes	yes	no	yes	yes
Robustness	yes	yes	no	yes	yes

[1]Also called Trueness
[2]Also called Intra-assay precision
[3]Recognizes ICH

traditional biological methods.

Biotechnological Methods

Biotechnological methods are used for large molecule (high molecular weight compounds) characterization for which traditional HPLC, GC and other chemical methods are not sufficient due to the complexity of the molecule being analyzed. These products are often derived through the fermentation and purification from biological organisms. Biotechnology includes products derived from cell cultures initiated from characterized cell banks and products derived from *in vitro* cell cultures, such as interferons, monoclonal antibodies and recombinant DNA-derived products. The methods used to determine the effectiveness and safety of these medicinal products are more complex and require different validation considerations in proving their suitability of use.

Biotechnologically derived products are more susceptible to contamination from infectious or pathogenic viruses because of the way they are derived. Viral clearance is concerned with evaluation of the viral safety of these products. There are three principle approaches to control potential viral contamination. The first approach is selecting and testing cell lines and other raw materials for the absence of infectious or pathogenic viruses. The second approach is to assess the capability of the production process to remove or inactivate these contaminants. The third option is to test the drug product at appropriate steps of the production process and assure the absence of the viruses.

Protein analytical techniques can be used to assess the amino acid or DNA sequence of the protein and its structural confirmation. Data from nucleic acid analysis may be useful since protein analytical methods may not detect all changes in protein structure resulting from mutations in the sequence coding for the recombinant protein. Analytical methods should be validated for the purpose of confirming the specific sequence of interest. The accompanying validation documentation, at a minimum, should include estimates of the limit of detection for variant sequences. Cell substrate characterization is the characterization and testing of banked cell substrates, which are critical components in the control of biotechnological drug products. The objective of this testing is to confirm the identity, purity and suitability of the cell substrate for manufacturing use.

Assays for biological activity, methods for analysis of the biological drug substance and quantitation of degradation products should be considered for determining the stability of the biotechnological product over time. The stability evaluation of these products may necessitate complex analytical methodologies. Since the active components of biotechnological products are typically proteins and/or polypeptides, the maintenance of molecular confirmation and, consequently, biological activity, is dependent on covalent and noncovalent interactions. In order to assure maintenance of biological activity during validation and storage, stringent handling requirements are necessary to avoid degradation of the molecule. A stability-indicating profile should be established to provide assurance that changes in the identity, potency and purity of the drug product are detected. The following are some of ➤

Table 4: Summary of Biological Method Validation Sources

Test	ICH	USP	Ph. Eur.	JP	FDA
Antimicrobial Effectiveness	Q6	yes	yes	yes	Yes
Sterility	Q6	yes	yes	yes	Yes
Microbial Limits	Q6	yes	yes	yes	Yes
Bacterial Endotoxin	Q6	yes	yes	yes	Yes
Pyrogen	no	yes	yes	yes	no
Rapid Micro Methods	no	yes	yes	no	PAT

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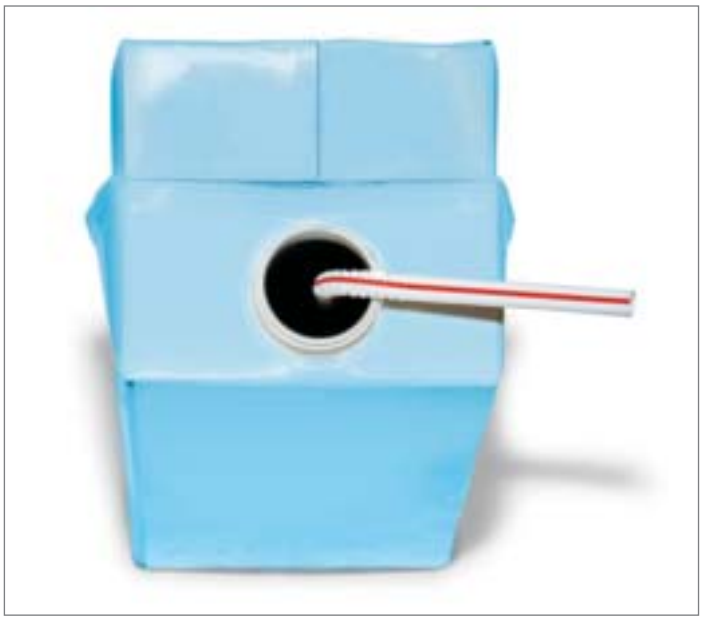

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the attributes that should be considered in demonstrating product stability, however, others attributes may be considered depending on the particular molecule under evaluation:

- Potency (biological activity)
- Purity
- Molecular characterization
- Appearance
- Visible particulates (in solutions)
- pH
- Moisture
- Sterility
- Excipients

Orthogonal testing approaches may be required for potency and purity testing due to inherent difficulties in achieving definitive results from single methodologies. Characterization of a biotechnological drug product includes determination of physico-chemical properties, biological activity, immunochemical properties, purity and impurities. Analytical procedures that are used for drug product release shall be validated for their intended use. *Table 5* (below) indicates the sources of information where more detailed validation requirements for biotechnological products may be located.

Physical methods

Physical methods are technique-dependent tests that are independent of the material or sample being analyzed. The majority of physical test methods fall into two broad categories: direct physical measurement or visual (organoleptic) inspection of a sample attribute. Physical test methods of either type are usually not validated in the traditional meaning. These methods often employ equipment that must be calibrated before measurements can be taken and recorded. Qualification procedures specific to the instrument or the analyst should be available. Analysts should be properly trained and qualified on the instruments before performing any analyses.

Direct physical measurements are measurements that are conducted on the sample. The results are reported without further transformation. Examples of typical direct physical measurements include length, mass, density, conductivity, force, pH, etc. The instrumentation used for these measurements should be qualified using written procedures. Procedures may include instrument and operational qualification as well as calibration or standardization traceable to recognized standards, such as those supplied by the National Institute of Standards and Technologies (NIST). Calibration of the instruments used to make physical measurements assures accuracy of the measurement to be taken. The precision of instruments like gauges can be documented through repeatability and reproducibility studies. The validation parameters of accuracy and precision are satisfied through qualification and calibration of the instruments used to make these direct physical measurements.

Visual tests are inspection methods that employ the sense of sight to detect either acceptable or unacceptable attributes of a sample. These tests are inherently subjective because they rely on human perception. To minimize their subjectivity the analyst must be trained to recognize acceptable and unacceptable attributes. The use of simulated flawed samples for comparison to the actual test sample aids in identifying sample defects. In addition, the analyst should not have a problem with the sense that is to be used for the analysis. An example would be if the test is a visual color exam then the analyst should not suffer from colorblindness. The authors recognize there are other organoleptic methods besides visual detection however, due to analyst safety concerns these are not considered suitable for use in the pharmaceutical industry.

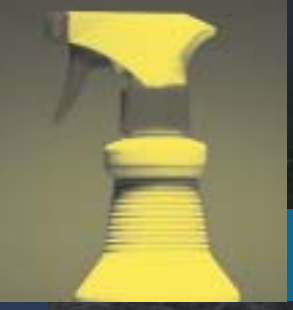
Pharmacopeial and Regulatory Support

Many companies test materials and products using the official specifications and methods published in the pharmacopeias. The question always arises regarding the validation status of the compendial monographs. The simple answer to the question, "Are compendial methods validated?" is, "Yes." The more accurate answer is the methods in the pharmacopeias are validated to requirements that were in force at the time the monograph was developed and submitted to

continued on page 28

Table 5: Summary of Biological Method Validation Sources

Parameter	ICH	USP	Ph. Eur.	JP	FDA
Viral Clearance	Q5A(R1)	Yes	Yes	Yes	See ICH
DNA Analysis	Q5B	Yes	Yes	No	See ICH
Stability	Q5C	Yes	Yes	No	See ICH
Cell Substrate Characterization	Q5D	Yes	Yes	No	See ICH
Methods for Batch Release	Q2(R1), Q5C, Q6B	Yes	Yes	No	See ICH



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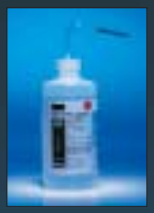
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October 15-16, 2007
2007 PDA Visual Inspections Workshop
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October 29-November 2, 2007
PDA's 2nd Annual Global Conference on Pharmaceutical Microbiology
(Conference, Courses and Exhibition)
Bethesda, Maryland

November 1-2, 2007
PDA/FDA Co-sponsored Conference Series on Quality Systems
Bethesda, Maryland

November 6-8, 2007
PDA Extractables/Leachables Forum
Bethesda, Maryland

April 14-18, 2007
PDA 2008 Annual Meeting
(Conference, Courses and Exhibition)
Colorado Springs, Colorado

May 19-23, 2008
2008 PDA Biennial Training Conference
(Conference, Courses and Exhibition)
New Orleans, Louisiana

Training

Lab and Lecture events are held at PDA TRI, Bethesda, Maryland unless otherwise indicated.

Lab Courses

October 1-5, 2007
Rapid Microbiological Methods

October 17-18, 2007
An Introduction to Visual Inspection

October 23-24, 2007
Fundamentals of D, F and z Value Analysis

October 25-26, 2007
Validating a Steam Sterilizer

October 31-November 2, 2007
Advanced Environmental Mycology Identification Workshop

November 13-16, 2007
Validation by Design (R): DoE Basics for PAT Applications

November 14-16, 2007
Developing an Environmental Monitoring Program

November 14-16, 2007
Pharmaceutical Water System Microbiology

December 5-6, 2007
Developing and Validating a Cleaning and Disinfection Program for Controlled Environments

Lecture Courses

October 8-10, 2007
Advanced Pharmaceutical Filtrations and Filters

October 29-31, 2007
Managing Quality Systems

Course Series

October 15-17, 2007
Philadelphia Training Course Series
Philadelphia, Pennsylvania

November 27-29
San Diego Course Series
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Chapters

September 27, 2007
Delaware Valley Chapter
EMEA Considerations and Vendor Night

October 11, 2007
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October 17, 2007
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(Conference, Courses and Exhibition)
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December 4-6,2007
Practical Aspects of Aseptic Processing
Basel, Switzerland

December 12-14, 2007
Dublin, Ireland Training Course Series
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February 18-21, 2008
2008 PDA/EMEA Joint Conference
Budapest, Hungary

Asia-Pacific

September 23, 2007
Japan Chapter
Sterilized Product GMP

November 13-14, 2007
Japan Chapter
Chapter Annual Meeting

December 2007
Japan Chapter
Sterilized Product GMP

Method Validation: An Overview of Global Standards, continued from page 24

the compendial authorities. Older monographs, while still validated, may not comply with the current standards.

The Ph. Eur., USP–NF and the JP include language in their respective publications concerning the validation status of the methodology that constitutes an official standard. The Ph. Eur. states, "The procedures for the tests and assays published in the individual monographs have been validated according to current practice at the time of their elaboration for the purpose for which they are intended." Similarly, the JP indicates, "When an analytical procedure is to be newly carried in the Japanese Pharmacopoeia, when a test carried in the Japanese Pharmacopoeia is to be revised, and when the test carried in the Japanese Pharmacopœia is to be replaced with a new test according to regulations in General Notices, analytical procedures employed for these tests should be validated according to this document." The USP–NF addresses the issue by stating, "Recognizing the legal status of the USP and NF standards, it is essential, therefore, that proposals for adoption of a new or revised compendial analytical procedures be supported by sufficient laboratory data to document their validity" and "The text of this information chapter harmonizes, to the extent possible, with the Tripartite International Conference on Harmonisation (ICH) documents Validation of Analytical Procedures and the Methodology extension text, which are concerned with analytical procedures included as part of registration applications submitted within the EC, Japan and the USA." The USP–NF also addresses the validation of biological methods in their General Chapter <1227>, "Validation of Microbial Recovery from Pharmacopeial Articles."

The authority of USP–NF methods are also recognized in section 501. [351](b) of the Federal Food, Drug and Cosmetic Act, which can be synopsized as indicating assays and specification in monographs of the *United States Pharmacopeia* and the *National Formulary*, constitute legal standards. Section 211.194(a)(2) of the *Code of Federal Regulations* (Subpart J, "Laboratory Records") instructs that the validity of the methods used in the laboratory must be documented as follows: "A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the *United States Pharmacopeia, National Formulary, AOAC INTERNATIONAL, Book of Methods* or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use."

International recognition of the validity of compendial methods is realized through language contained in the ICH guidelines Q6A, *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* and Q6B, *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products*. Q6A indicates, "References to certain procedures are found in pharmacopoeias in each region. Wherever they are appropriate, pharmacopoeial procedures should be utilized"; Q6B states, "Pharmacopoeias contain important requirements pertaining to certain analytical procedures and acceptance criteria which, where relevant, are part of the evaluation of either the drug substance or drug product."

The recognition that compendial methods are validated does not alleviate manufacturers from verifying these standards are appropriate for their product, using their equipment as tested by their laboratories. To address this gap, the USP–NF has recently published General Chapter <1226>, "Verification of Compendial Procedures," which will become official on December 1, 2007. This chapter provides general guidance regarding the documented objective evidence required to establish the suitability of compendial methods "under actual conditions of use. In the United States, this requirement is established in 21 CFR 211.194(a)(2) of the current Good Manufacturing Practice regulations…"

Conclusion

The available information regarding the requirements for validating methods is abundant. In order to satisfy global validation requirements, users must recognize that test methods are wide-ranging and the appropriate validation supporting method use must meet the specific challenges of each method. Specifications should be established early in the process because they are needed to identify the method validation parameters and appropriate acceptance criteria for assessing safety, efficacy and purity. The intent of the validation is to provide evidence that the chosen methods meet regulatory requirements and are appropriate for their intended use in determining product quality.

References

A number of sources were researched during the preparation of this article and are cited within the document. A complete list of sources referenced by the authors, including those not cited in the text, is included with the online version of this article at www.pda.org/pdaletter.

July/August Top 10 Bestsellers

PDA Parenteral Drug Association

1. **Pharmaceutical Quality Control Microbiology: A Guidebook to the Basics**
   By Scott Sutton, PhD
   Item No. 17242, PDA Member $210, Nonmember $260
2. **PDA Technical Report 1, Revised 2007, Validation of Moist Heat Sterilization Processes Cycle Design, Development, Qualification and Ongoing Control**
   Item No. 01001, PDA Member $150, Nonmember $250
3. **Environmental Monitoring: A Comprehensive Handbook, Volume I, Volume II, and Protocol CD**
   Edited by Jeanne Moldenhauer, PhD
   Item No. 17239, PDA Member $530, Nonmember $659
4. **Validation of Analytical Methods for Biopharmaceuticals: A Guide to Risk-Based Validation and Implementation Strategies**
   By Stephan O. Krause, PhD
   Item No. 17264, PDA Member $255, Nonmember $315
5. **Systems Based Inspection for Pharmaceutical Manufacturers**
   Edited by Jeanne Moldenhauer, PhD
   Item No. 17243, PDA Member $255, Nonmember $319
6. **Risk Assessment and Risk Management in the Pharmaceutical Industry: Clear and Simple**
   By James L. Vesper
   Item No. 17219, PDA Member $235, Nonmember $289
7. **Microbiology in Pharmaceutical Manufacturing - 40% Off**
   Edited by Richard Prince
   Item No. 17185, PDA Member $285, Nonmember $359
8. **PDA Archive on CD-Rom – PDA Archive Retrieval Index**
   Item No. 01101, PDA Member $395, Nonmember $590
9. **Risk-Based Software Validation: Ten East Steps - 40% Off**
   By David Nettleton and Janet Gough
   Item No. 17256, PDA Member $200, Nonmember $249
10. **Pharmaceutical Contamination Control: Practical Strategies for Compliance**
    Edited by Nigel Halls, PhD
    Item No. 17246, PDA Member $255, Nonmember $315

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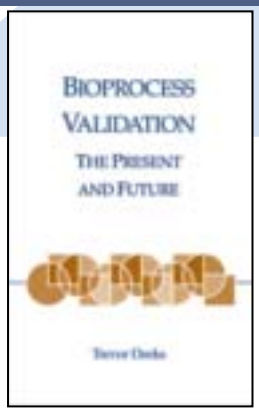

PDA-DHI Publication

Bioprocess Validation: The Present and Future
by Trevor Deeks

This book explains process understanding and what part it plays in the validation effort that is required in order to register a new product or process. The tools to do this are becoming more readily available and the regulatory environment is changing to permit this. This guidebook examines the current norms and status of bioprocess validation and explains how to establish compliant process robustness, ensuring consistency and thereby assuring product quality.

2007. ISBN: 1-933722-16-9

Item No. 17248
Member: US$ 225
Nonmember: US$ 279

Two New Multimedia Training CD Programs for Auditors and Management

FDA's Guide to Inspections of Lyophilization of Parenterals
dated June 11, 2007
A Compliance program and inspection guidelines
Item No. 11085, Member US$ 300, Nonmember US$ 360

A System Based Quality and Compliance Due Diligence Audit Training
A system evaluation of a firm for senior management.
Item No. 11084, Member US$ 300, Nonmember US$ 360

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Quality & Regulatory *Snapshot*

Communicating Quality & Regulatory Activities

Rich Levy, PhD, PDA

With the introduction of the Science and Technology Snapshot four issues ago, PDA made a commitment to improving the visibility of the work our members do on a regular basis to enhance our industry's performance. This month, we are introducing a new feature to the *PDA Letter*—the **Quality and Regulatory Snapshot.** This monthly snapshot will provide news and updates of PDA's activities in the quality and regulatory affairs area, as well as report on other items of importance in the global quality and regulatory arena.

In this initial Snapshot, we provide an update on PDA Task Force activities in the preparation of Association comments on ICH Q10 and an EMEA proposal addressing the contents of the Batch Release Certificate for Investigational Medicinal Products. In addition, we report on the work PDA did to support EMEA in its efforts to understand the industry's feelings on the positions articulated in its reflection paper on the discretion of a Qualified Person to deal with minor deviations associated with the production of pharmaceutical products. Finally, we provide an update on a special task force activities related to EMEA's new guideline *Virus Safety Evaluation of Biotechnological Investigational Medicinal Products,* which was formed per a special EMEA request to comment. This project is demonstrative of PDA's ongoing effort to establish and maintain relationships with regulatory bodies to facilitate constructive dialogue between industry and government. As you can see, this will be a global forum.

I hope you find this new feature useful. We understand the need to let our members know what we're involved with, as well as provide you timely and useful information. Over the course of the year, we will provide you with feedback opportunities to let us know how we are doing. In the meantime, if you have topics you think we should include in a future column or any other feedback, please email us at snapshot@pda.org.

Task Force *Update*

Q10: Pharmaceutical Quality System

Earlier this year, the International Conference on Harmonisation (ICH) moved their Q10 guidance document on quality systems to Step 2 of the approval process. At this step, ICH requests comments from the public. This is done by having the document posted for comment by the regulatory authorities in each ICH region (Europe, United States and Japan). This has already been done by the U.S. FDA (comments due October 11, 2007) and Europe (comments due November 30, 2007).

In anticipation of this, PDA had organized a task force to develop its comments on the Q10 guidance. The task force, under the leadership of **Louise Johnson,** is currently in the process of finalizing these comments.

EMEA: Contents of Batch Release Certificate for IMPs

The European Medicines Agency (EMEA) recently published a proposal for the content of the Batch Release Certificate for Investigational Medicinal Products (clinical trial materials). A PDA task force, chaired by **Karen Ginsbury**, Pharmaceutical Consulting Israel, reviewed the proposal and developed PDA comments, addressing the impact on comparators and placebos and the need to keep studies blinded. At press time, the comments are being reviewed by the PDA Regulatory Affairs and Quality Committee (RAQC) and will also be reviewed by the PDA Board of Directors before submission to the EMEA. Watch www.pda.org and the *PDA Letter* for the final version of the PDA comments.

Regulatory *Relations*

One of the most important benefits of PDA membership is the ability to participate in the regulatory process through task forces aimed at commenting on regulatory initiatives and programs and meetings meant to generate dialogue between government and industry. Because PDA's members have a reputation for their ability to synthesize sound science with public regulatory standards, the Association is occasionally asked to provide special commentary on specific regulatory initiatives.

EMEA's BWP Requests Info

In June, the EMEA's Biologics Working Party (BWP) requested that PDA participate in further scientific discussions on its draft guideline *Virus Safety Evaluation of Biotechnological Investigational Medicinal Products.* The European Federation of Pharmaceutical Industries and Associations (EFPIA), EuropaBio and the European Generic Medicines Association also were invited to participate. Invitations were extended based on the comments submitted by PDA and the other organizations during the public consultation period for the draft guideline in 2006.

PDA's comments were submitted December 28, 2006 (see the Feb. *PDA Letter*, p. 28, and www.pda.org/regulatorycomments). The comments document was prepared by a PDA task force composed of volunteers from the PDA Biotechnology Advisory Board (BioAB) and the Regulatory Affairs & Quality Committee (RAQC). This collaborative effort between BioAB and RAQC marks an effort to ensure that both PDA's science experts and regulatory experts contribute to regulatory guidance moving forward.

The letter sent along with the comments to EMEA in December opened the door to further discussion: "PDA would be pleased to meet with the BWP to discuss our comments and would also be willing to attend and/or co-sponsor a public meeting to hear and understand the concerns of BWP and to jointly work with BWP on proposed alternative wording," the task force offered in the letter.

Responding to the BWP's request, PDA reconvened a 20-member task force to consider the following topics for further discussion:

- Under what circumstances, and why, it might be appropriate not to test EOP cells as recommended in the guideline.
- Under what circumstances, and why, it might be appropriate not to complete virus clearance studies prior to initiation of phase III studies; what particular aspects of [ICH] Q5A need not be addressed at this point in time, and, in the opinion of industry, what minimum data would assure the viral safety of phase III material.
- The factors that should be taken into consideration in a risk-based approach to assuring viral safety and the factors that are not pertinent.
- The application of a risk-based approach for the viral safety of a novel cell line.

Seven of the 20 task force members are meeting on September 12 in London to discuss these issues with representatives of the aforementioned associations and the BWP. The PDA representatives are talking with representatives of EFPI and the European Biopharmaceutical Enterprises on September 11 to find common ground prior to the meeting with BWP on the twelfth.

EMEA: QP Discretion – Survey

PDA has collected survey results on the EMEA Reflection Paper on QP Discretion for Dealing with Minor Deviations. At press time, the survey results were being approved by the PDA RAQC and the Board of Directors. The survey results were derived from a questionnaire using verbatim questions provided by the EMEA. The results generally supported the value of the reflection paper and endorsed inclusion in Annex 16 of the EU GMP Guide covering the Qualified Person. The reflection paper will be discussed at the EMEA Interested Parties Meeting on September 26, 2007, in London. PDA attendees at the meeting will be **Jim Lyda** and **Stephan Roenninger,** Roche, Basel.

Tell Us What You Think

Let us know what you think of this and all articles in the month's issue. Contact morris@pda.org and we will publish your remarks in an upcoming issue!

ZLG: The Voice of Germany's Inspection Services

An Interview with Sabine Paris, PhD

Jim Lyda, PDA

[**Editor's Note:** Jim visited the ZLG offices in Bonn, Germany, on July 16 and met with **Sabine Paris, PhD**, Head of the Medicinal Products Department, to discuss the role of ZLG, current issues and current opportunities. A history of ZLG is included with the online version of this article at www.pda.org/pdaletter.]

Lyda: What does ZLG stand for?

Paris: "Zentralstelle der Laender fur Gesundheitschutz bei Arzneimitteln und Medizinprodukten." In English, this translates to the "Central Authority of the Laender (Federal States) for Health Protection Regarding Medicinal Products and Medical Devices."

Lyda: Can you tell me how you came to ZLG?

Paris: I earned my PhD in analytical chemistry at the University of Muenster and worked for nine years in the pharmaceutical industry, primarily in regulatory and medical affairs. I was interested in working in Bonn for a number of reasons and was fortunate to be selected for this position when my predecessor moved on.

Lyda: I was not familiar with ZLG until recently. Some of my colleagues have told me the same thing.

Paris: ZLG is relatively new compared to the other government regulatory functions in Germany. It was created in the 1990s to satisfy harmonization requirements for medical devices. It was expanded to the pharmaceutical area in 1999, and now serves as the major contact and coordination point for the pharmaceutical inspectorates in Germany, as well as the major European and international contact point.

Sabine Paris, PhD

Lyda: What is the relationship of ZLG to BfArM and PEI? What is the role of each in inspections?

Paris: BfArM and PEI are both federal authorities under the jurisdiction of the German Federal Ministry of Health (BMG). BfArM is the Federal Institute for Medicinal Products and

continued on page 36

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How Will Inspectors View Risk Management?

Jim Lyda, PDA

The Pharmaceutical Inspection Cooperation Scheme (PIC/S) has taken the first steps to define future training on quality risk management (QRM) for PIC/S member inspectorates. On July 2-3, PIC/S hosted the inaugural meeting of their new Expert Circle on Quality Risk Management at the headquarters of Afssaps, the French health authority, in Paris. The meeting, which was a brainstorming session, was led by PIC/S Chairman **Jacques Morenas,** Afssaps, and included about 30 inspectors from most of the PIC/S members. PDA and ISPE representatives attended the closing session on July 3.

Following is an informal report of the meeting, outlining the current thinking of some inspectors and future activities for inspector training. PDA was represented by **Jan Gustafsson,** PhD, Novo Nordisk; **Peter Reichert,** Novo Nordisk; **Stephan Roenninger,** PhD, Roche; and **Jim Lyda,** PDA.

The Expert Circle will focus on quality risk management rather than the more limited activity of quality risk assessment. The Expert Circle's goals are to provide:

1. Training framework for the future, including a seminar program for inspectors on principles, tools and examples related to QRM
2. Inspection system and models for inspectors
3. Communications system for facilitating application of QRM, including networking with industry

These goals will allow inspectors to have a better understanding of the principles of QRM and acceptance of common definitions based on ICH Q9. The Expert Circle will also provide information on the main QRM tools and examples of their use by industry. The group will likely host workshops with industry participation to focus on manufacturing issues and examples from industry of different tools it has used (Failure Modes and Effects Analysis, Hazard Analysis and Critical Control Points, etc). The Expert Circle is interested in input from smaller companies to show the kind of problems they will be facing.

There was discussion on the value of quantitative data in QRM decision making, with some of the inspectors suggesting there should be maximum use of data when it is available. There was a general industry view that much of the QRM approach will be qualitative. Failures are rarely repeated but are unexpected events. The most valuable activity is to get the correct team members involved in the process early on. It was noted that companies have much data that should be converted into knowledge. Most problems that cause a fatality are caused by human error; yet, there is a perception that industry did not view risk management as covering human error.

PIC/S notes that QRM is an ongoing activity and will be subject to continuous improvement and evolution. There is need for a forum that will allow high-level, systematic, philosophical information exchange on the use and value of QRM. This would not be a question and answer forum but a true exchange of information and a healthy, risk-free discussion between the inspectorates and external/industry experts.

Watch the *PDA Letter* for future developments in the PIC/S approach to QRM. For more information on PIC/S, visit www.picscheme.org.

Quality Systems: An Evolving Environment

Program Co-Chairs: Zena Kaufman, Abbott Laboratories, and Steve Mendivil, Amgen

One unique characteristic of the pharmaceutical and biopharmaceutical industry and the people who are part of it, is the wealth of discussions that exist on quality-related matters. These discussions are unique because they often combine quality concepts and technical matters, encased within regulatory expectations. Having the opportunity to discuss, share and benchmark, links the industry back to the collective goal of providing quality medicines to patients around the world.

The industry has also evolved from quality control to quality assurance to quality management, and is now moving towards a harmonized quality systems approach. A quality systems approach is not new; however, framing quality systems in a pharmaceutical context is.

Over the past 25 years, this industry has changed dramatically. It has moved from companies with plants that supply local markets to multinational companies with plants that supply the world. It has moved from solely paper-based systems to systems that rely to varying degrees on information technology solutions. The diversity in technologies has grown to include biotechnology products and combination products, in addition to more traditional dosage forms.

A quality systems approach is not new; however, framing quality systems in a pharmaceutical context is.

All of these forces point to the necessity of integrated pharmaceutical quality systems over the life cycle of industry products. Quality risk management tools must be integrated to define what is critical and where to focus our resources. Knowledge management tools should be used to leverage prior learning into global knowledge. Quality systems must be augmented with these tools to improve how deviations are corrected and prevented from recurring, to monitor processes and develop process knowledge, to effectively manage change at manufacturing sites and, most importantly, to keep management informed and engaged.

Please join PDA on November 1-2, 2007, at the PDA/FDA Co-Sponsored Conference on Quality Systems in Bethesda, Md. The meeting will feature some of the leading experts in this field, both from regulatory agencies and industry, who will share their insights and real-time examples of practical solutions.

ZLG: The Voice of Germany's Inspection Services, An Interview with Sabine Paris, PhD, continued from page 32

Medical Devices, which has tasks in the field of human drugs, medical devices and narcotics. PEI is the Paul-Ehrlich Institute, or the Federal Institute for sera, vaccines and tissue preparations. BfArM and PEI operate somewhat like CDER and CBER do in the U.S. FDA. Both are responsible for review of their products for safety and efficacy, and both are involved in the initial or preapproval inspections of the products they regulate.

In the field of health protection, the German Federal States, or Laender, are in charge of the enforcement of all applicable legislation. That's why for drug supervision, the GMP inspections fall under the responsibility of the states. Thus, ZLG, by comparison, is not part of BMG, but gets its authority under the treaty between the 16 states, the Laender, and is accountable to the states for support and authority. Of course, there is an effective relationship between the inspectorates, ZLG and the federal authorities. Once products are approved for marketing, the inspectorates of the states, together with the OMCLs (official medicines control labs), are responsible for GMP inspections, the issuance of GMP certificates, authorization of manufacturers and importers, export certificates and drug testing. Regarding special products, e.g., tissue preparations, experts from BfArM and PEI may participate in GMP inspections as experts.

ZLG is responsible for a number of coordinating tasks and cooperates with the higher federal authorities in the Benchmarking of European Medicines Agencies (BEMA), as well as different European and international issues and surveys.

Lyda: Germany is the largest member state in Europe, with a large and well-known pharmaceutical industry. Lyda: How many inspectors are there in Germany?

Paris: There are almost exactly 100 inspectors who are represented by ZLG. They are located in the 16 states, or Laender, and operate under the procedures and policies of the state health authorities. In some states, such as Bayern (Munich, Germany) and North Rhine-Westfalia (Cologne, Germany), there is a large drug industry, thus a large number of inspectors. Other states have only a single inspector.

Lyda: German inspectors, like the MHRA, do a large number of inspections outside of Europe, including in the United States. Why is this?

Paris: This is due to a special national regulation laid down in Section 72a German Drug Law. In summary, the import of medicinal products or active substances which are of human, animal or microbial origin, or are active substances manufactured using genetic engineering, from countries not belonging to the European Union/European Economic Area (EEA) or not being Mutual Recognition Agreements-partners is only possible after the competent authority (for the importer) has certified the GMP compliance of the third country site. The certification can only be issued after an on-site inspection has been carried out by the competent authority itself or another EU/EEA inspectorate.

Lyda: What is your relationship to PIC/S?

Paris: Germany is an active member of PIC/S, and ZLG acts as the representative of the German GMP Inspection Services. I personally joined the PIC/S Committee of Officials this year and will be attending more of the PIC/S functions in the coming years. I also want to mention here that I represent the German inspectorates at the EMEA ad hoc GMP Inspection Services meetings as well.

Lyda: What are the issues that concern you right now when you look out from your ZLG chair? What are the local and international issues that you see as challenges for the future?

Paris: There are several. One of the main issues we are discussing right now is the implementation of ICH Q9: *Quality Risk Management* from the perspective of the inspectors. It is the same for the future of ICH Q10, which relates to quality systems. How will these guidances be implemented by the industry, and how will the inspectors review these activities? This brings up the entire issue of inspector training. These guidances will also impact the industry, and we found during our discussions on dedicated facilities that the industry was also not always prepared for a proper risk-management approach. On both sides, we have something to learn. The upcoming changes in the Variations Regulations (covering changes to a manufacturing process) will also impact these issues. So this is clearly a challenge for the future as we are at the beginning.

Another important task is the fight against counterfeits and related illegal activities. Recently the European Commission Taxation and Customs Union published a summary of community customs activities on counterfeit and piracy, showing a large increase in interceptions of illegal products entering the European Union in 2006. Several initiatives have already started on a European, as well as on an international level [World Health Organization (WHO) Impact Task Force]. In the future, it will be important to pull all the authorities together to be more effective. This problem shows up particularly through use of the Internet. Here in ZLG, we will set up a central monitoring function and will be hiring an additional expert to conduct Internet research for illegal activities. This issue will be with us for many years to come.

An additional area is the implementation of the new tissue law, both in

Germany and the entire European Union. There will be efforts to harmonize the standards and inspections surrounding tissues for medical uses and the procedures for inspecting them. On a European level, there are draft guidance documents being prepared at this time for this purpose [within the European Union Standards and Training in the Inspection of Tissue Establishments (EUSTITE)]. So this will be a new area for all of the inspectorates in the European Union, and it is important to have a harmonized approach on how we do this. There are similar issues associated with the Advanced Therapies Regulations to be adopted in the European Union, and this will be a major topic of change and review for all of us in Europe for some time to come.

Finally, it seems we are not at the end of the discussion of API regulation in Europe. The European Parliament had a written declaration that both producers and importers of active principles should submit a certificate of good manufacturing practice delivered by the European authorities following mandatory inspection at the site of production. If this comes to pass, there will be a whole new series of inspections of API manufacturers around the world. This will be quite a large increase in the workload.

Lyda: What message would you like to send to our readers about ZLG?

Paris: The establishment of ZLG has led to a higher level of transparency and has further promoted the international effectiveness and cooperation of the German GMP Inspection Services. ZLG has developed as an indispensable service point for the federal states, as well as for other stakeholders. This is also reflected by the enormous popularity of our website (www.zlg.de) that had 4.2 million visits in 2006, which corresponds to 11,500 per day.

We also believe that cooperation and information sharing between the regulators and the industry is important for a high-quality drug supply and for the patient. Cooperation will probably be most useful in the areas of training for inspectors, especially in those areas where there is new technology. This might be in the area of real-time courses or video materials, which can be shared with the inspectorates. For new inspectors, industry input will also be helpful for training in the basic production areas.

There is also value in sharing GMP issues in a broader way between the inspectors and the industry, especially for topics that are easily solved. The industry may have the most resources and systems to help with such a process. For example, we picked up a recommendation from industry that was helpful in the use of the WHO pharmaceutical certificates and the German harmonization with that system. This is a good example of concrete problem solving, rather than asking different inspectors for their interpretation. For the history of ZLG, please view the online version of this article at www.pda.org/pdaletter.

Membership Committee to Optimize the PDA Member Experience

Lindsay Donofrio, PDA

While reviewing PDA's organizational model, the subcommittee on Governance and Structure of the Board of Directors' Strategic Planning Committee found that the Association did not have a committee of volunteers dedicated to the member experience. Appropriate groups focusing on science, technology and regulatory information—the Science Advisory Board, the Biotechnology Advisory Board and the Regulatory Affairs and Quality Committee—are in place, along with committees for chapters and programs—the Chapter Council and the Program Advisory Board.

"We have all of these groups, but there was a hole," said PDA Chair-Elect **John Shabushnig**. "And the one hole we found was that there really wasn't a committee focusing on membership."

To fill this void, Shabushnig and a team of PDA members began working with **Nahid Kiani,** V.P., Membership Services and Sales, to establish the Membership Committee. The committee will focus on optimizing the PDA member experience and generating enthusiasm around volunteerism. "We have identified some activities that are important to both attracting new members and retaining existing members," said Shabushnig. "Events like the New Member Breakfast provide opportunities for experienced members to connect with new members, making PDA a more personal experience."

The committee will be a cross section of new and veteran members, including experts from a variety of fields in the pharmaceutical industry. "This is really the goal of the group," commented Shabushnig. "We're looking for a globally diverse team of people that is creative and will bring new and fresh ideas to the membership experience."

The Membership Committee is open to all PDA members. "We want

Volunteer Spotlight

Name: John Shabushnig, PhD

Company: Pfizer Inc

Title: Sr. Manager, Quality Systems and Technical Support

Education: BS, Chemistry, Carroll College; PhD, Analytical Chemistry, Indiana University

PDA Join Date: 1992

Areas of PDA Volunteerism: Past PDA Director and current Board of Directors Chair-Elect, current Executive Committee Member, current Science Advisory Board Member, current Visual Inspection Interest Group Leader, current Visual Inspection Forum Program Co-Chair, past Annual Meeting Program Committee Member and Co-Chair, current Strategic Planning Committee Member and Chair, current Awards Committee Member, current Nominating Committee Member, speaker and moderator at numerous PDA meetings.

Professional Awards Won:

- Pfizer Colleague Recognition Award for developing and delivering training in microbiology, aseptic processing and sterilization technology
- Pharmacia & Upjohn Special Recognition Award for Visual Defect Definition and Classification Team
- Upjohn Quality Control Academy
- Carroll College President's Society
- Jane Tichy Award, presented to outstanding graduate in chemistry from Carroll College

Interesting Fact about Yourself:
I am a member of the Highpointers—attempting to climb to the highest geographic point in all 50 states. Have successfully summitted 41 (plus Puerto Rico and the District of Columbia) thus far.

Of your PDA experiences, which stand out the most?
It has to be the people I have met over the years as a member of PDA. From the early days when we were forming the first interest groups, the staff and fellow PDA members have always been there to support these and many other activities. Russ Madsen in particular was always there to help. I appreciate the global reach of PDA, and have also enjoyed interacting with our PDA members in Japan, especially on the subject of visual inspection. There has never been a shortage of talented and willing volunteers. Since those early days, I have made many new friends through PDA. We have worked together to advance our industry, to bring good science to our methods and regulations, and to have fun in doing so.

Which member benefit do you most look forward to?
I find the *PDA Journal of Pharmaceutical Science and Technology* and the PDA technical reports to be a great aid in my work. They allow me to remain current as the science and technology continues to advance at an ever increasing pace. I routinely use the CD-ROM archives to access these articles and reports. The online member directory is also a wonderful tool to help stay in contact with fellow members.

Which PDA event/training course is your favorite?
I have to say the Visual Inspection Forum, since this meeting and subject matter are unique to PDA and of great interest to me. I was actively involved in the creation of this meeting in 2000 and have continued to help organize it each year since. I also greatly enjoy the Annual Meeting. It is an excellent opportunity to reconnect with friends and colleagues and to survey current work on a broad range of topics.

How has PDA benefited you professionally?
Pfizer has been a strong supporter of my involvement in PDA. My involvement has increased my ability to contribute to the company and to the industry, and this has been recognized. PDA has also provided a forum to present our scientific results and to constructively engage our regulators around the globe.

PDA Chair-Elect John Shabushnig, PhD, (right) is working with PDA's membership team, Nahid Kiani, V.P., (center) and Hassana Howe, Senior Coordinator, (left) to launch the recently established Membership Committee.

to open this committee up to the membership as an opportunity to get involved at the grass-roots level and help shape the PDA experience," said Shabushnig. "The committee gets at the idea that there are different ways and different kinds of volunteer experiences that you can have as a PDA member."

"For me," continued Shabushnig, "if I look at PDA, the whole experience is really interpersonal, so this is an opportunity to make sure we are doing all we can to make the membership experience very positive. It's the individual experiences and relationships that allow the members to achieve the scientific and the regulatory standards the Association is capable of and has demonstrated in the past."

"PDA recognizes that the strength of the Association is its members. When members get involved, the PDA community prospers," said Kiani. "In order to ensure the Membership Committee meets its goals, the staff on PDA's membership team will support and execute new initiatives as they develop."

If you have ever thought about joining a PDA committee, here is your chance! The Membership Committee offers an ideal opportunity to get more involved with PDA, and the only qualification for participating is that you are an energetic supporter of PDA.

Please take the time today to become active within your PDA community. To volunteer, fill out the volunteer form inserted in the envelope with your *PDA Letter*. For more information on volunteering with PDA, visit www.pda.org/getinvolved.

Delaware Valley Chapter Showcases Student Science Projects

Sue Vogt Speth, GlaxoSmithKline

The PDA Delaware Valley Chapter (PDADV) hosted an evening of educational events on Wednesday, June 13, 2007. One hundred and thirty participants from local pharmaceutical and biopharmaceutical companies attended the event at the Desmond Hotel and Conference Center in Malvern, Pa.

During the meeting, the Delaware Valley Science Fair finalists presented their projects and were honored with awards. **Traute Ryan,** PDADV Student Committee Chair, announced the following PDADV Science Fair award recipients and their projects:

Emily McGettigan (12th grade), **Kyle Tretina** (12th grade), **Natania Field** (11th grade), **James Chen** (10th grade), **Cristy DeObaldia** (9th grade), **Jenny Guidera** (8th grade)

After the students' presentations, three members of the Temple QA/RA program spoke on various aspects of aseptic processing.

In "Trends in Sterile Product Manufacturing Facilities," **Dan Casaburi** discussed the past 20 years of industry changes, which have led to reduction in sterility risk from the days of simple scale-up to the modern automated facility.

Frank Diana, PhD, presented "Process Development in Aseptic Processing." Diana provided attendees insight on balancing many factors in designing, optimizing and scaling up a formulation and process in order to develop products that meet patient requirements.

Peter Smith, PhD, explained the IND process used in R&D with an emphasis on risk- based initiatives and how these initiatives are incorporated into the submission process in his talk, "Pharmaceutical Quality Assurance in Aseptic Processing: Submissions."

Following the presentations, the speakers entertained questions and shared ideas with meeting attendees.

For information on the Delaware Valley Chapter's upcoming events, please visit www.pdadelval.org.

Who's Who

Dan Casaburi, Regulatory Product Manager, sanofi pasteur

Frank Diana, PhD, Senior Director, Technical Operations, Endo Pharmaceuticals

Sue Vogt Speth, Delaware Valley Chapter Operating Committee Member; Senior QA Specialist, GlaxoSmithKline

Peter Smith, PhD, President, Research Quality Assurance

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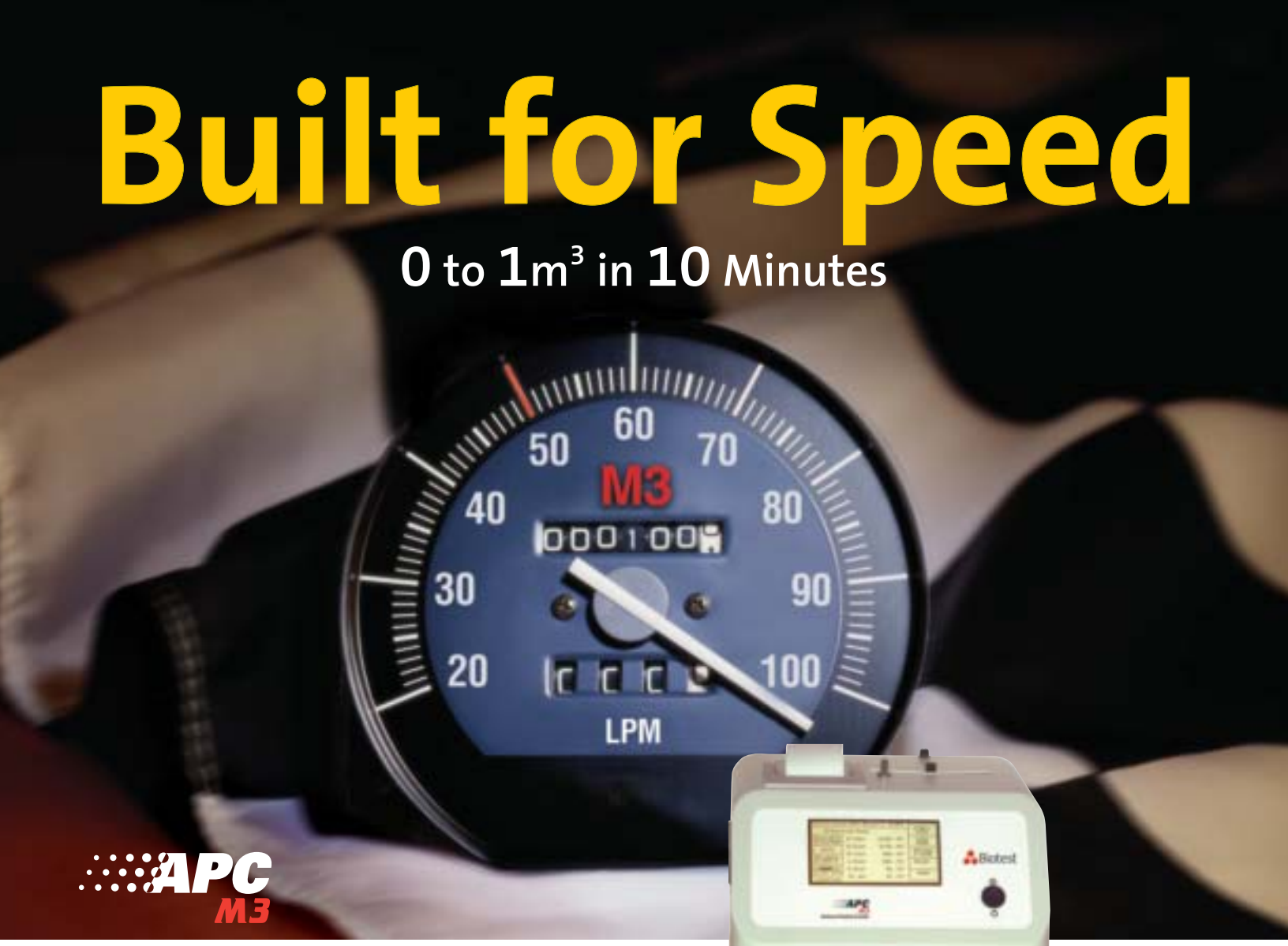

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Visit us at the 2nd Annual Global Conference on Pharmaceutical Microbiology, October 29–30, 2007 — Table 1

New England Chapter Meeting Focuses on Filtration

Louis Zaczkiewicz, Hyaluron Contract Manufacturing

The PDA New England Chapter (NEPDA) held its third meeting of the year on June 13, 2007, highlighting filtration of liquids and gasses. The evening included a tour of Millipore, a networking reception with the event sponsors, presentations on Technical Report No. 26, *Sterilization Filtration of Liquids,* and Technical Report No. 40, *Sterilizing Filtration of Gases,* and a post-meeting wrap-up.

The evening started with tours of the Millipore validation laboratory and the bioprocess manufacturing sciences group laboratory in Billerica, Ma. Guides showed attendees how Millipore conducts test studies on their customers' products using filters to determine flow rate, capacity, compatibility, sterility assurance and bacterial retention in the validation laboratory. In the bioprocess laboratory, an area about the size of a high school gymnasium housed a fantastic collection of vessels, filtration units, pumps, controls, winches and CIP apparatus, along with the support utilities to easily handle the needs of start-up and big pharmaceutical companies. Here customers also work with Millipore application engineers to experiment with new concepts.

During a one-hour networking session, attendees met and discussed their needs with the meeting sponsors: Chisholm Corporation/Pall, Sartorius Stedim Biotech, Millipore, High Purity New England/Meissner (filtration suppliers and distributors) and Hyaluron Contract Manufacturing (fill-finish company). With the support of the event's sponsors, the Chapter was able to provide appetizers and drinks to networking participants.

Once meeting participants were seated for dinner, chapter leaders presented a brief introduction to PDA, announced upcoming chapter events and encouraged attendees to get more involved.

Maryellen Brown introduced the evening's first speaker, **Jerold Martin,** who presented "PDA TR-26 Sterilizing Filtration of Liquids – An Overview and Update." **Mark Sitcoske** introduced the second speaker, **Leesa McBurnie,** who presented "PDA TR-40 Sterilizing Filtration of Gases – A Comparison with TR-26." Both presentations are available for viewing on the chapter page of the PDA website (www.pda.org/chapters).

Between the two speakers, **Myron Dittmer** gave special appreciation to Past-President **Mark Staples,** PhD, who received the PDA Chapter Volunteer Award at the 2007 PDA Annual Meeting for his significant contributions to PDA and the New England Chapter over the past 20 years. At the end of the meeting, speakers were joined by **Maurice Phelan,** Co-Chairman of the Technical Report No. 26 Revision Committee, to informally discuss the evening's presentations and field questions on the new revision scheduled for completion this year.

The NEPDA organizing committee, Global PDA, event sponsors and the hotel staff helped the chapter meet its networking and education goals, making the evening a success. Later this year and into the following years, NEPDA events will focus on PDA's technical reports. PDA currently has 37 technical reports, with more on the way and some in revision, that provide industry consensus guidance on subjects of interest to the FDA-regulated industry. All PDA members receive new technical reports as they are released. Older technical reports can be purchased through the PDA website.

Who's Who

Maryellen Brown, Marketing Specialist, Chisholm Corporation

Myron Dittmer, New England Chapter Member-at-Large; Owner & Principal Consultant, MFD & Associates

Jerold Martin, Senior Vice President, Scientific Affairs, Pall Life Sciences

Leesa McBurnie, Senior Microbiologist, Meissner Filtration Products

Maurice Phelan, Director, Regulatory Affairs and Services, Millipore

Mark Sitcoske, President, High Purity New England

Mark Staples, PhD, New England Chapter Past-President; Vice President, Research and Development, MicroCHIPS

Louis Zaczkiewicz, New England Chapter President; Engineering Director, Hyaluron Contract Manufacturing

Chapter Contacts

The following is a list of the PDA Chapters, organized by the regions of the world in which they are located. Included are the Chapter name, the area(s) served, the Chapter contact person and his or her email address. Where applicable, the Chapter's website is listed. More information on PDA Chapters is available at www.pda.org/chapters.

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PDA Welcomes New Members

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Colin Abercrombie, Genzyme

Laura Abrams, GlaxoSmithKline

Nidia Acevedo ReComS Group

Cindy Adams, Northampton Community College

Mitsuaki Aizawa, Kissei Pharmaceutical

Franklin Akomeah, Johns Hopkins University

Juergen Anklam, Vetter Pharma Fertigung

Lytle Apryl, Ben Venue Laboratories

Stephanie Aquin, Philip Morris International

Esther Arkadash, Bio-Technology General

Marcy Armstrong, Merck

Charles Arnold, CSL Behring

Martin Bagnall, Sampling Technologies

Anu Bansal, Eli Lilly

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If your information appears inaccurate in this list, please visit www.pda.org to update your profile or email changes to info@pda.org.

PDA's Prefilled Syringes Universe Expanding

Berlin, Germany • November 27 – 30, 2007 • www.pda.org/europe

Conference Co-Chairs: Brigitte Reutter-Haerle, Vetter Pharma, and Dietmar Weitzel, PhD, Novartis

Prefilled syringes are becoming the parenteral packaging system and delivery method of choice. The advantages in convenience and security for health care professionals and consumers are well-known. In addition, reduced overfill and reduced waste are so notable that the market for products in prefilled syringes continues to grow at rates beyond 10% annually.

The Universe of Prefilled Syringes & Injection Devices Conference will bring together pharmaceutical scientists, suppliers and manufacturers, who contribute to successful development and manufacturing. There will be presentations on practical technical, scientific and regulatory aspects. Also, issues related to product development and life-cycle management will be discussed. Experts from all areas of the industries involved in prefilled syringes will give updates on the current situation and address the challenges on the horizon.

The conference will cover the following topics:

- Quality, materials, methods and technologies
- Development, manufacturing and process technology
- Supplier qualification issues
- Elastomers
- Regulatory and compliance aspects
- Case studies
- Alternative applications for parenterals

On behalf of the Program Committee, we invite you to The Universe of Prefilled Syringes & Injection Devices Conference on November 27-28, 2007, in Berlin. Don't miss this opportunity to learn about the latest developments in parenteral applications and network with colleagues and experts from the various industries involved in developing and manufacturing prefilled syringes. There will also be an exhibition and a poster session, and, for the first time, there will be two training courses on prefilled syringes. One will cover aspects of development and the other course will focus on regulatory topics.

We look forward to an exciting conference, which will help you to faster and better exploit the opportunities with prefilled syringes.

Faces and Places

PDA Pharmaceutical Cold Chain Management Conference
Bethesda, Maryland • June 13 – 14, 2007

Plenary Session 1: Pharmaceutical Cold Chain Discussion Group and TR-39: (l-r) Conference Chair Rafik Bishara, PhD; Bob Dana, PDA; and Wigand Weirich, F. Hoffmann-La Roche

Plenary Session 2: Global Regulatory Requirements: (l-r) Ian Holloway, MHRA; Barry Rothman, FDA; Rosa Motta, FDA; Moderator Robert Seevers, PhD, Eli Lilly; Jeanne Taborsky, USP; and Vincent Tong, Health Canada

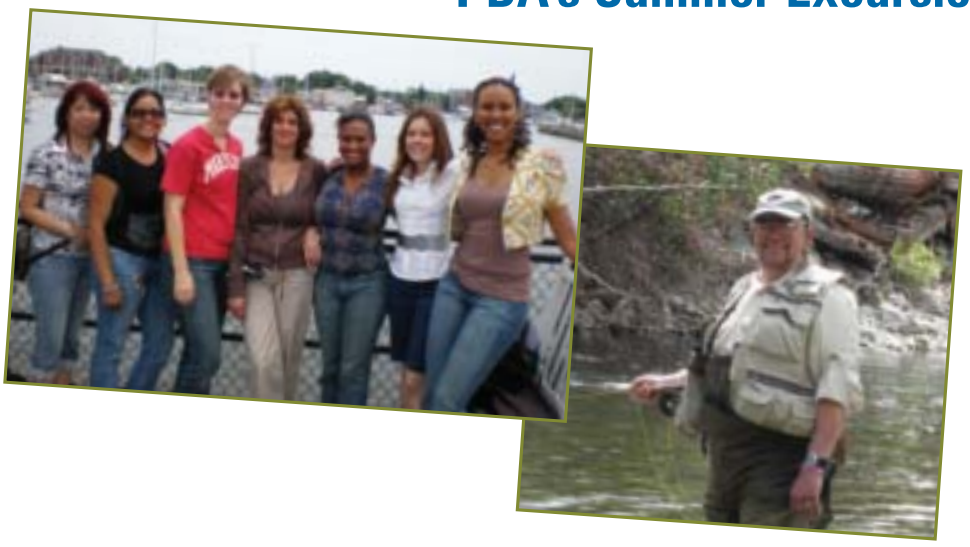
Meeting attendees enjoy lunch in the exhibit hall

Plenary Session 3: U.S.-Based Mail Order Management: (l-r) Christine Chadler, Department of Veterans Affairs; Moderator David Ulrich, Abbott Laboratories; and Mike Zeglinski, Pharmacare

Plenary Session 6: Interaction of Packaging Components for Risk Management of Temperature-Controlled Pharmaceuticals: (l-r) Jean Vezina, University of Florida; Moderator Jean-Pierre Emond, PhD, University of Florida; and Alex Salomon, Evidencia

Plenary Session 8: Support of Service Providers to TR-39: (l-r) Mark Maurice, Sensitech; Kevin O'Donnell, ThermoSafe Brands; Larry Gordon, Cold Chain Technologies; and Moderator Dave Ray, Sensitech

PDA's Summer Excursions



(Top left) PDA's Membership Services and Sales team after a long day of crabbing on the Chesapeake Bay: (l-r) Janny Chua, Andrea Viera, Emily Alesantrino, Nahid Kiani, Cindy Tabb, Hassana Howe and TaMela Jeffries (In reality, the group was on a team-building retreat in Annapolis, Md.)

(Bottom right) PDA's Bob Dana *is actually* fly fishng near his Sun Valley, Idaho, home.

TRI TALK

TRI Finalizes Move to Bethesda, Sign Up Now!

Gail Sherman, PDA

What to write about? So much happening! By the time you read this, we will be safely ensconced in our new space in Bethesda, Md., having hurdled the challenges that go along with moving. We spent the past several months throwing or giving away ten-years worth of "stuff," some of which we did not know we had and some of which we couldn't even identify! Even after cleaning out the Baltimore facility, we still managed to fill four trucks with lab equipment and boxes. Once in Bethesda, we spent the next few weeks getting organized and ready for our first classes in early August (see photos below). Now it's time for you to visit us at our new location. If you had ever been to Baltimore, you certainly will not recognize what has been built in Bethesda!

What else are we doing? Of course, we are running laboratory courses—the "Aseptic Processing Training Program" is full for 2007, and we have opened registration for 2008. We are also running some new lab courses in addition to our traditional ones. New this autumn are: "Developing an Environmental Monitoring Program," "Pharmaceutical Water Systems Microbiology," "Validation by Design: DoE Basics for PAT Applications" and "Downstream Processing: Separations, Purifications and Virus Removal." We are currently working on the 2008 laboratory schedule, so be on the look out for more new course offerings next year.

On the lecture side, we are offering courses throughout the autumn in conjunction with PDA conferences, including the PDA/FDA Joint Regulatory Conference (September), the PDA Visual Inspection Forum (October) and PDA's 2nd Annual Global Conference on Pharmaceutical Microbiology

John Brecker, Fleet Laboratories, instructs the first course at the new TRI facility in Bethesda. Ten students attended the sold-out "Environmental Mycology Identification Workshop" on August 2-3.

(October). Stand-alone course series will bring TRI learning to both U.S. coasts, with one planned for Philadelphia and one for San Diego. In our new Bethesda facility, we will be offering "Advanced Pharmaceutical Filters and Filtration" and a new course "Managing Quality Systems."

We will be very active in Europe this autumn as well, presenting courses along with the following PDA meetings: Pharmaceutical Cold Chain Management (October) and The Universe of Prefilled Syringes (November). We will also offer stand-alone course series in Berlin and Cork, Ireland, (November) and in Dublin (December). Special thanks to the PDA Ireland Chapter for their support in developing the Dublin Course Series.

And lastly, I want to express our appreciation to all of those folks out there who donated equipment and materials to keep TRI running for another ten years. Without you, we couldn't have done it.

Look for photos of our new facility and a list of donors in coming issues. Please stop by and pay us a visit!

Conference Report

France Chapter Event Examines Good Practices for Investigational Medicinal Products

Karen Ginsbury, Pharmaceutical Consulting Israel; Carina Sonnega, PhD, Biotechnology Consulting; and Volker Eck, PhD, PDA

On May 3-4, 2007, PDA held a fascinating chapter conference in Lyon, France, on a topic that is currently a challenge for the pharmaceutical industry: GMP and Investigational Medicinal Products (IMPs). Bearing in mind the disparity of approaches to investigational drugs between the United States and the European Union, and even differences between states within the European Community, this conference provided participants the opportunity to hear expert opinions on the implementation of incremental GMPs, while simultaneously complying with GLPs and GCPs.

The meeting was highly interactive with numerous question and answer sessions and a large amount of input from participants as well as speakers. During the breakfast session, two captivating presentations were given on the use of disposable vials and small-scale equipment for pilot studies. Breaks and social activities were filled with additional informal chats, which allowed PDA members to discover the role of the regulators in doing their utmost to ensure the safety (GMP aspects) and comparability (at later stages of trials) of investigational products to be released for human use.

The program was divided according to the stages of development that a novel product undergoes, including outsourcing issues, GLPs and preclinical development, animals to humans (early GMPs), Phase IIa – III, and control of the clinical trials supply chain.

PDA France Chapter President **Jean-Louis Saubion,** who provided an introduction to the topic, opened the conference. He explained the role of the Qualified Person (QP) in Europe, as opposed to Quality Assurance in the United States, for batch manufacturing and control oversight and release of investigational medicinal products in accordance with Annex 16.

Several QPs provided insights on problems they have encountered, such as:

- Temperature deviations during shipment of IMPs
- The challenges of changes during manufacture and control of investigational products
- Distinguishing process deviations from natural process fluctuations while handling a limited process and product knowledge base, e.g., during Phase I production of product

Miguel Sanchez, Head of the Inspection Department, Afssaps (the French health authority), gave an interesting and highly relevant presentation titled "The IMPD Guideline and Regulatory Expectations and Observations in Europe," allowing participants to gain an insider's view of how the Agency implements and interprets the directive.

Luciano Gambini, Director, QA, Nerviano Medical Sciences, Italy, gave a thought-provoking lecture that clearly and concisely showed the interface between GLPs, GCPs and GMPs. After a lengthy question and answer session, the general opinion of participants was that additional and more practical guidance might be needed in this area. Participants agreed that clinical investigators and CROs are often very familiar with GLP and GCP regulations, but generally they have little, if any, knowledge of GMP regulations. This is one area where the pharmaceutical/biotech industry might need to be more proactive in order to ensure, for example, compliance with shipping and storage requirements.

Two presentations discussed the EU Investigational Medicinal Products Directive (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/18540104en.pdf) and its implications within the industry, as compared to the U.S. FDA's draft guidance on GMPs for production of Phase I clinical trials materials.

A Call for Action

The following action points came out of the conference:

1. A need for a follow up conference to provide additional information on gray areas and emerging issues. PDA is already working on this program, which is scheduled for January 23-24, 2008. Mark your calendars and keep an eye on www.pda.org for registration details.
2. A need for additional and more practical guidance beyond what the regulators have provided is necessary. PDA had already initiated preparation of a technical report on GMPs for investigational medicinal products.

In general, the program content was evaluated by participants as extremely high-quality. Thank you to all members of the organizing committee and, of course, to conference participants, who contributed to the usefulness and success of this meeting.

Upcoming Meeting

Conference to Discuss Fundamentals of Freeze and Spray Drying

Cologne, Germany • September 11 – 13, 2007 • www.pda.org/europe

Conference Chair Harald Stahl, PhD, Niro Pharma Systems

On behalf of the Program Planning Committee, I would like to invite you to the 2007 PDA **Pharmaceutical Freeze Drying and Spray Drying Technology Conference** on September 11-13, 2007, in Cologne, Germany.

Increasing the shelf life of parenterals is an important task in pharmaceutical R&D, as well as in full-scale production. Freeze drying and spray drying offer the possibility to convert, in a controlled way, liquid formulations into more stable powders. Participants in this conference will have the opportunity to join colleagues and experts from around the world to learn the fundamentals of these technologies, as well as to share experiences about industrial applications.

We have planned a well-rounded program to provide attendees with a wealth of information, learning opportunities and an environment that stimulates discussion. The speakers, who are scientists with hands-on experience, will lead the following presentations:

- Freeze Drying in the Pharmaceutical Environment
- Head Space Detection of Water Vapor and Gases
- Challenges in a Freeze Dryer Project
- Development of Freeze Drying Processes Using PAT Technologies
- What is the Status? Where Can Spray Drying be Used?
- Spray Drying Overview Development and Process
- Supercritical Spray Drying – First Results with Proteins
- Manufacture of cGMP Stable Suspension Vaccines by Aseptic Apyrogenic Spray Drying

On day two, we will visit the GEA Lyophil facility, one of the most prominent manufacturers of freeze dryers. On day three, there will be a hands-on training course on the development of a freeze drying cycle.

We look forward to seeing you in September in Berlin.

October 9-11, 2007
Cleanrooms/Isolators/RBS
Berlin, Germany

October 17, 2007
Pharmaceutical Cold Chain Management
Berlin, Germany

October 25, 2007
Supplier Quality and Global cGMPs
Rome, Italy

November 8, 2007
United Kingdom Chapter
TR-1 Workshop

November 13-15, 2007
Berlin Training Course Series
Berlin, Germany

November 15-16, 2007
Cork Training Course Series
Cork, Ireland

December 4-6, 2007
Practical Aspects of Aseptic Processing
Basel, Switzerland

Chapters and People

UK Chapter Transition

The new UK Chapter President, **Siegfried Schmitt,** PhD, Principal Consultant, PAREXEL Consulting, extends a handshake to outgoing President, **Frank Talbot,** Managing Partner, FT Pharma Services. PDA sends a big "Thank You" to Frank for his many years of commitment to the Association. Frank will remain on the UK Chapter board as past president. We look forward to working with Siegfried in his new role as the UK Chapter President.

(Left to right) Siegfried Schmitt, PhD, and Frank Talbot

R³Nordic Annual Conference

May 14-15 • Oslo, Norway

Seen here are attendees at the R³Nordic Annual Conference gala event in Oslo, May 14-15, 2007. On behalf of PDA, Sr. V.P. Georg Roessling, PhD, presented a Berlin "Bear" to the R³Nordic committee, signifying the long friendship and good relations between the two organizations. (Left to right) Georg Roessling, PhD; Arild Svendsen; Bengt Ljungqvist, PhD; Torgier Stenstad Booth; Berit Reinmuller, PhD; Rich Levy, PhD; and Lennart Hultberg.

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After evaluating 25 vendors, the European Medicines Agency (EMEA) selects TrackWise as its enterprise Quality Management System (QMS).

Claus Christiansen...
Integrated Quality Management Auditor for the EMEA,
gave these reasons for the selection:

- "Quick and smooth implementation."
- "Overall breadth of the TrackWise solution."
- "Ease of configuration."
- "Ability to integrate with existing software."
- "Audit trail and electronic signature."
- "Pharmaceutical industry experience."
- "Manages critical quality processes and global risk analysis."

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ABOUT THE EMEA

The European Medicines Agency coordinates the evaluation and supervision of medicinal products for its 25 European Union (EU) member states. It has implemented TrackWise to replace paper based and spreadsheet systems used by the agency to manage its quality processes. Implementation took only four months, meeting set timetables and budget goals.

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