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PDA Letter

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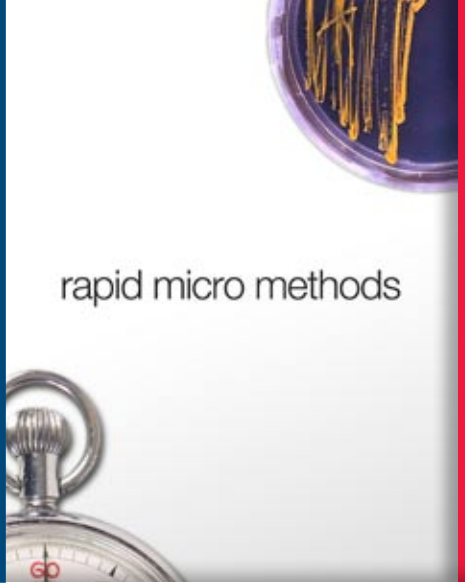

In This Issue:

PDA Parenteral Drug Association

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It's Time to Get Rapid!

Michael J. Miller, PhD, Microbiology Consultants, LLC

When PDA *Technical Report No. 33 Evaluation, Validation and Implementation of New Microbiological Testing Methods* was first published in 2000, it was assumed that the pharmaceutical and biopharmaceutical industry would recognize and accept the benefits of implementing rapid microbiological methods (RMM) as an alternative to conventional, growth-based methods and to utilize the technical report as a roadmap for qualification and implementation strategies. Although a number of firms have implemented RMM platforms for a variety of in-process and finished product release tests, the mass exodus from conventional methods has not occurred as quickly as originally anticipated. It is important to fully understand the reasons for the industry's hesitancy because it has been demonstrated that RMMs can contribute to the continuous improvement and capability of pharmaceutical processes, encourage manufacturing efficiencies and agility, and enhance the quality of drug products throughout their life cycle. A recent survey suggests that we continue to express apprehension about the cost, validation and regulatory acceptance for implementing RMMs.[1] If we are to effectively move away from 19th century microbiology methods and embrace currently-available 21st century technologies, it is necessary to explore each of these concerns and provide clarity around what is perception, what is reality and what might be just operating with our eyes wide shut.

Is There Really An Issue With Cost?

There are obvious costs involved with the purchase, qualification and implementation of RMMs. Depending on the capital expense, the manner in which the system will be employed and the process required to adequately validate the system for its intended use, the cost associated with implementing a RMM can be significant. However, it is imperative that the potential end-user comprehends the bigger picture; namely, the costs associated with the existing method, the costs associated with the initial RMM investment and the long-term financial benefits or savings that the RMM may provide. A number of economic models are available that can easily calculate the return on investment, payback period and net present value when implementing a RMM, and I recently reported significant cost savings over a five year period when implementing an automated environmental monitoring (EM) RMM the (BioVigilant® IMD-A™) as an alternative to manual, active air sampling.[2] In this example, the elimination of sampling and testing resources, lab space and lab equipment, and the ability to immediately react to an EM excursion instead of three to five days after the event provided sufficient economic justification to

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Cover art:
According to some industry experts, the time for implementing Rapid Microbiological Methods is now. Cover by James Austin Spangle.

Coming Next Issue:
PDA Journal: New Editor, New Online Format

Editor's Message

Why Change a Good thing?

What do isolators, PAT and rapid microbiological methods have in common, and what do they tell us about the pharmaceutical industry?

Well, the commonalities include:

1. These technology arrays offer manufacturers improved ways of manufacturing and/or controlling the quality of pharmaceutical products.
2. The implementation of each is supported, if not promoted, by some or all of the major regulatory agencies.
3. Industry has been slow to adopt these technologies, for various and good reasons.

The history of these technologies shows that the pharmaceutical industry is conservative when it comes to manufacturing its products. Whether that caution derives from regulatory concerns/fears, financial considerations or from other reasons, the fact is, it takes lot for industry to change a good thing.

According to cover story author Michael Miller, it is time to get rapid with respect to microbiology testing. It is totally understandable why firms remain wedded to the traditional clean room or traditional process controls, all of which aren't particularly old technologies. But when one considers that traditional microbiological tests predate WWI, one must wonder if Michael is right, maybe it is time to get rapid. Also in this issue, the "Technology Trend" in the "Science & Technology Snapshot" takes a look at some of the rapid micro methods (RMMs) presented at the *PDA's 3rd Annual Global Conference on Pharmaceutical Microbiology.* An article in "Quality & Regulatory Affairs" reports on CBER's draft guidance on validating growth-based RMMs; the document is still in the revision stage following public comment.

"Faces and Places" is back with photos from recent PDA meetings and a PQRI working group gathering at PDA headquarters.

Correction: A "PDA News & Notes" article in the February 2009 issue should have said that new PDA Sr. Vice President of TRI and Regulatory Affairs Bob Dana will report directly to President Bob Myers with a dotted line to Sr. Vice President of Scientific and Regulatory Affairs Rich Levy.

PDA Letter

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Accomplishments, Achievements Surround PDA

CHAIR'S MESSAGE

John G. Shabushnig, PhD

This has been a hard winter for many. Both the weather and the economic climate have been impacting our personal and professional lives. I know I am looking forward to spring! Spring also means it is time for our annual meeting. The Program Committee and staff have been working hard to deliver another interesting and informative event.

I am happy to report a number of recent and significant accomplishments for PDA. As always we are focused on maximizing service and value to you, our members.

The Training and Research Institute (TRI) continues to expand its course offerings. The two-week Aseptic Processing Course is the cornerstone of the curriculum at TRI. A one-week Advanced Aseptic Course is now available to complement this offering. It has been designed for graduates of the two-week Aseptic Processing Course or (with instructor approval) for those who are actively involved with aseptic processing operations and have significant experience in this area. In addition, the faculty and staff are now available to deliver custom training in your facility. This can be a cost-effective way to improve the skills of a large number of colleagues. If you have not had the opportunity to attend a course at TRI, or just visit the facility in Bethesda, I highly recommend it.

The search for our next President is going well. We received a good response to my request for resumes from interested members and associates which went out at the beginning of the year. I am impressed (but not surprised) by the talent and experience within our association and am confident that we will have a new staff leader in place by mid-year. Please also mark your calendar to attend a celebration of **Bob Myers**' many contributions to PDA at the PDA/FDA Joint Regulatory Meeting in September.

You may have noticed the move to electronic distribution of our publications. You have asked for this service and it is being rapidly implemented. The *International Pharmaceutical Quality* went electronic last fall and the *PDA Journal of Pharmaceutical Science and Technology* has just begun electronic distribution. An enhanced version of Journal access (including access to past issues and search capability) is expected to go live later this year. The *PDA Letter* has been available in both hardcopy and electronic form for some time. We have a full pipeline of Technical Reports for 2009, including both new subject matter (e.g., Single Use Systems) and updates to previously published TR's (e.g., *TR No. 3 Validation of Dry Heat Processes used for Sterilization and Depyrogenation*).

The Chapter Council has also been working hard to complete the *PDA Chapter Handbook*. This document will help guide the formation and operation of local PDA chapters. The chapters are the grassroots of our association and continue to be the first contact with PDA for many. I am especially excited about the formation of our first student chapters. The New England and Southeast chapters have taken the lead in this new initiative.

Finally, there is a full calendar of events in Europe, capped by the PDA/EMEA meeting in Berlin this October. This is truly a unique meeting, offering insight into the European regulatory process not available in any other forum. Don't miss it!

I look forward to seeing you in Las Vegas, Berlin or at another PDA event this year.

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The next generation of new technologies, therapies and medicines are emerging. Looking forward five years, there could be many revolutionary treatments of a number of diseases or injuries, such as cancer or muscular dystrophy, skin in burn victims or Alzheimer's. These innovative biotechnological treatments include Advanced Therapy products based on gene therapy, cell therapies and new vaccines such as those based on poxvirus. These medicines have a huge potential for patients and industry but present many scientific, technical and regulatory challenges for their industrialization. This conference will focus on the technology driving these new therapies and will look at how these 21st century medicines will be developed, manufactured and licensed within a rapidly changing pharmaceutical industry environment. The main topics addressed in presentation and workshops are:

New generation of biopharmaceutical processes · Bioanalytical challenges for developing IMPs · Development and licensing · Designing efficient lean processes · Process Design Space and robust processes · New single use manufacturing technologies and facility design.

Science & Technology *Snapshot*

Interim Journal Website Facilitates Online Access

Rich Levy, PhD, PDA

The interim website for the PDA Journal at www.pda.org/journal went live in March with the January/February issue, and the new page has been accessed more than 6,000 times in the two weeks following posting. While this launch can be considered successful, PDA wants to make it clear that we are earnestly working on a new, dynamic website with HighWire Press, scheduled to launch in mid-July. That website will be built from a HighWire Press template, which have a solid track record with a number of other HighWire Press journal partners.

PDA has selected a number of features that will add value for the PDA membership, including RSS (Really Simple Syndication) feeds and Microsoft PowerPoint downloads. RSS feeds benefit readers who want to subscribe to timely updates from the Journal website. The PowerPoint download tool will allow readers to easily create slides of graphics in Journal articles, complete with the appropriate copyright information. The site will be fully searchable, and access to an online archive will be available.

The January/February issue launched without a hitch, well, other than being a few weeks late. So far, the most frequently cited articles have been the two commentaries articles, one on the new EMEA position on reverse osmosis as a means of water for injection production and the other on the convergence of risk management, cGMPs and aseptic processing technology.

The March/April issue of the Journal is being prepared as this article goes to press, and will be available on the website by April. See the "Journal Preview" on the next page for more information on the articles to be published.

It is extremely important that all members update their email notifications from PDA so that they can receive updates when new Journals are posted. To customize your email notifications, go to www.pda.org/email.

Technical Report *Watch*

In Draft: *The Task Force developing the technical report has begun drafting the document or initiated the rewriting process. For most technical reports, several drafts are written before the document moves to "Global Review."*

- **Analytical Methods Validation (AMV)**
- **Fundamentals of a Cleaning and Disinfection Program**
- **TR-3 – Dry Heat Sterilization Revision**

In Global Review: *After the Task Force completes the their writing activities and the team is satisfied with the draft document, the draft TR is placed on the PDA web site and is made available for global member review – when the review is completed, Task Force members consider the feedback received and the resultant document moves on to final technical editing.*

- **Validation of Manual Aseptic Processes**

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

- **Moist Heat Sterilizer Systems: Design, Commissioning, Operation, Qualification and Maintenance**
- **TR-30 Parametric Release, 2009 Revision**
- **TR-22 (Revised), *Process Simulation Testing for Aseptically Filled Products***

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

- ***Blow-Fill Seal*** – back to BFSIOA and PDA Committee for Revisions
- ***Biological Indicators for Sporicidal Gassing Processes: Specification, Manufacture, Control and Use*** – Task Force addressing comments from SAB
- ***Points to Consider When Investigation Microbiological Data Deviations (MDD)*** – to Task Force for revisions
- ***Steam-In-Place*** (with SAB)

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

- **TR-15 (Revised), *Validation of Tangential Flow Filtration in a Biopharmaceutical Applications***

Technology *Trend*

Rapid Micro Methods Slowly Gain Ground

Walter Morris, PDA

Rapid microbiological methods (RMMs) are steadily gaining acceptance in the pharmaceutical industry as a viable alternative to traditional methods, although their uptake has been confined mostly to new products. Regulatory acceptance of the alternative methods and the challenge of comparing them to historic methods is one barrier to widespread use for legacy products.

Despite these challenges, the types of RMMs and their applications within the industry are growing, and the *PDA's 3rd Annual Global Conference on Pharmaceutical Microbiology* last October included a number of speaker presentations and posters on RMMs and their uses.

Nucleic-acid based methods using real-time PCR were highlighted in a number of posters and presentations.

A "comprehensive collaborative Ring Trial study" that included two different vendors and the cooperation of seven pharmaceutical companies in four countries was featured in a poster by Wyeth researcher **Brandye Michaels,** PhD.[1] The technology tested was the "Hygiene Screening System" (HSS) a multiplex real-time PCR developed by German-based Biotecon Diagnostics. According to the poster, the HSS is a fluorescence-coupled PCR technology for the qualitative detection of the bacterial genera *Staphylococcus, Micrococcus* and *Corynebacterium* within 90 minutes. The selection of these bacterial genera is key, according to the poster, because Biotecon Diagnostics had surveyed industry and found that "up to 80% of the microorganisms isolated from pharmaceutical facility personnel, air and surfaces belong to these three genera." The poster concluded that the HSS was highly accurate and precise method for the fast and reliable detection of the three bacterial genera, and that 30 samples could be processed in 1–1.5 hours. The poster extrapolated these results to an 80% decrease in conventional identification workflow. In addition, the poster reported that the system requires "limited labor/skill/lab space," its protocol and analysis is "relatively simple" and "capital investment is low."

The feasibility of using real-time PCR to analyze swabs was the subject of a poster by a group of Pfizer researchers: **Lin Chen, Michael Baumstein** and **Kendral Smith.**[2] The specific system evaluated was the MicroPro, a flow-cytometry based microbial detection technology which labels the microorganisms' DNA using fluorescent dye, developed by Advanced Analytical Technology,

continued on next page

Journal *Preview*

Moist Heat "Myth Busting"

Walter Morris, PDA

There's a popular television show in the United States called "MythBusters" that puts to the test popular beliefs and misconceptions, proving them right or wrong. Well, in the March/April issue of the PDA Journal, PDA's **James Agalloco, James Akers** and **Russell Madsen** do some mythbusting of their own with respect to moist heat sterilization in their commentary article, "Revisiting the Moist Heat Sterilization Myths." Who knows, maybe the article will inspire an episode of the television show!

As always, we encourage members to submit their opinions to the Journal for publication and also to respond to articles published. The new online format will help facilitate the dialogue. It is also allowing us to publish more articles per issue. This month's edition offers nine manuscripts, including two Technology/Application" articles and five research pieces.

Commentary

- J. Agalloco, J. Akers and R. Madsen, "Revisiting the Moist Heat Sterilization Myths"
- S. Saraf, "D. Singh, V.K. Dixit and S. Saraf, "Formulation Optimization of Serratiopeptidase-loaded PLGA Microspheres Using Selected Variables"

Research

- T.R. Saini and T. Nahata, " Formulation Optimization of Long-acting Depot Injection of Aripiprazole by Using D-optimal Mixture Design"
- J. Smith, M. Mehmi, L.J. Marshall, P.A. Lambert, "Evaluation of Disinfecting Procedures for Aseptic Transfer in Hospital Pharmacy Departments"
- B. Malaekeh-Nikouei and N. Davies, "Double Loading of Cyclosporine A in Liposomes Using Cyclodextrin Complexes"
- Z. Wen, A. Vance, F. Vega, X. Cao, B. Eu and R. Schulthesis, "Distribution of Silicone Oil in Prefilled Glass Syringes Probed with Optical and Spectroscopic Methods"
- D.K. Wang, L. Kong, J. Wang, X. He, X. Li and Y. Xiao, "Polymyxin E Sulfate-Loaded Liposome for Intravenous Use: Preparation, Lyophilization, and Toxicity Assessment In Vivo"

Technology/Applications

- V. Tsui, M.S. Somma and L.A. Zitzner, "Leachables Evaluation for Bulk Drug Substance"
- D. Corrigan, S. Piletsky and S. McCrossen, "Comparative Study of the Swabbing Properties of Seven Commercially Available Swab Materials for Cleaning Verification"

Technology Trend, continued from previous page

Inc. The researchers "screened different types of swabs, based upon the materials of construction (MOC) of the swab head as well as the head configuration (*e.g.,* shape, size, texture) to determine which swab head design provides for the lowest fluorescent background and therefore overall increased assay sensitivity on the MicroPRO." *Staphylococcus aureus* was used to examine several different swab types, and for one swab type (the BD BBL CultureSwab EZ) the MicroPRO can detect between 100–1000 CFU without pre-enrichment prior to processing. After repeating the testing on compendial organisms the team concluded, "as a new rapid microbiological technology, the MicroPRO has demonstrated the potential to be used for routine swab sample analysis that will enable for a quick sample turn-around." The team was concerned, however, with the detection limit between 100–1000 CFU/mL when tested directly on the MicroPRO system. "This degree of sensitivity will limit the usage of the MicroPRO to environments that have relatively high microbial counts." To increase the sensitivity of the system for processing swab samples with low microbial counts, the team suggested the use of an enrichment step prior to testing.

RMMs based on spectroscopy were also featured at the meeting.

The use of real-time PCR for virus detection was the topic of a presentation by Applied Biosystems **Mariela Cuadras,** who spoke about the results of a study performed using her firm's TaqMan® system during a session of the PDA microbiology conference.[3] The study examined the system's ability to detect and quantify viral nucleic acids in less than 4 hours. The study tested the system with the common human plasma contaminant, human Parvovirus B19, the FDA-recommended MVM Parvovirus and operator-introduced human Adenovirus. The study found that the

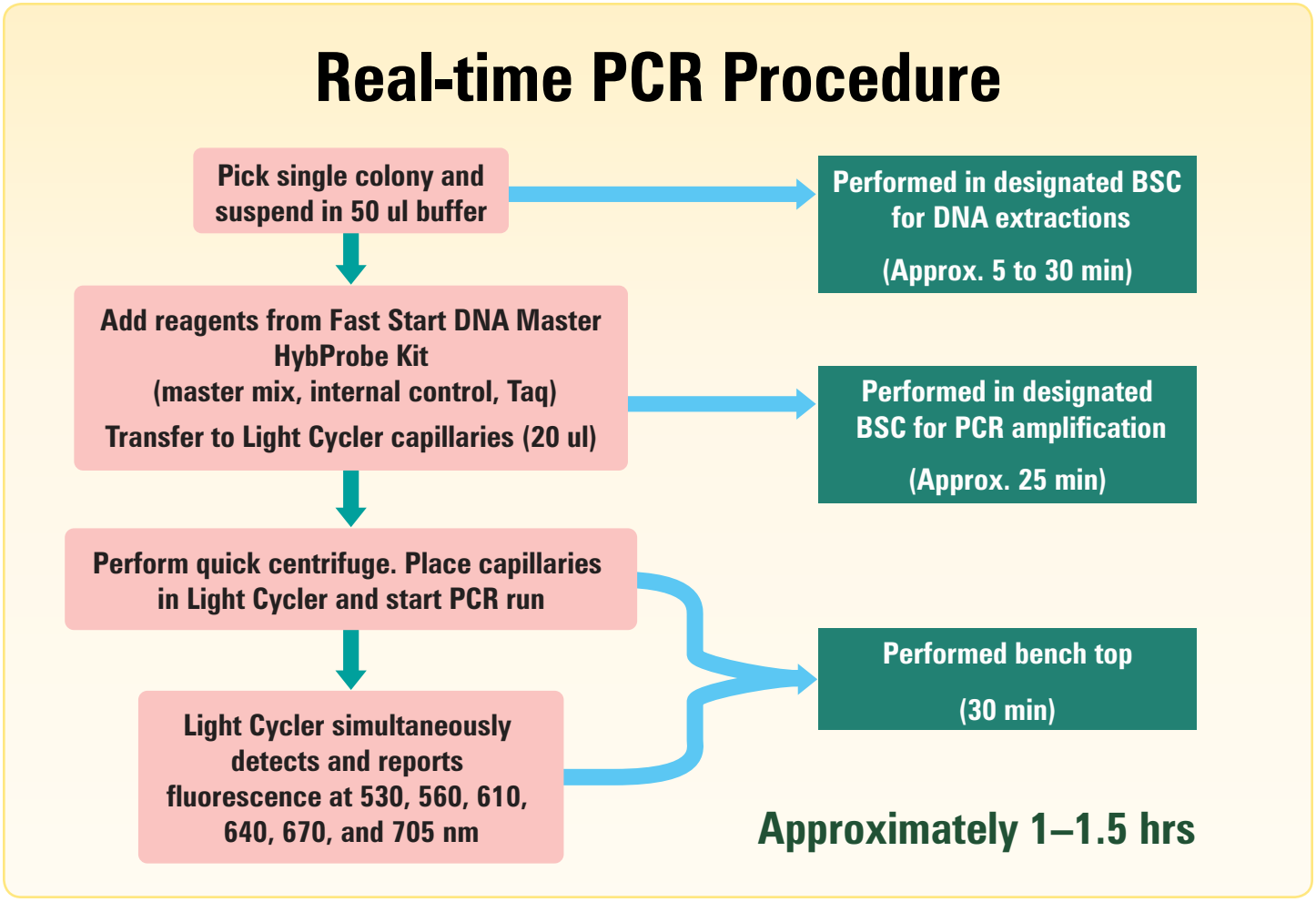

Figure 1: From poster by Brandye Michaels, PhD, Wyeth Biotech
Procedure depicted was developed using Biotecon Diagnostics "Hygiene Screening System" real-time PCR.

TaqMan system could "reproducibly detect a low copy number of target nucleic acid within a dynamic range of 6–8 Logs." The B19 and Adenovirus TaqMan assays did not cross-react with cellular DNA or DNA from related viruses. There was, however, limited cross-reactivity between MMV TaqMan assay and mouse DNA, but the researchers felt that this was "likely due to MMV infection in the donor mouse." The researchers identified a correlation in the level of viral clearance between real-time PCR and virus culture-based methods. Finally, they purported to obtain results in approximately 4 hours.

A growth-based RMM was put to the test and presented in a poster by another team from Pfizer. The group of **Claudio Denoya, Jennifer Reyes** and **Amelia Tait-Kamradt** from Pfizer Global Research tested the Pallcheck™ Rapid Microbiology System by Pall Life Sciences, which consists of "a relatively simple and portable luminometer and reagent kits," and allows for "direct measurement of microbial contamination on a membrane in liquid samples and on surfaces, as well as measurement of surface contamination using swabs." Filtered liquid samples provide "maximum sensitivity." An enrichment step was used "for critical applications where very low levels of contamination" were expected. The researchers concluded that the Pallcheck system "can be applied to multiple microbiology applications, such as bioburden for excipients and drug products."

RMMs based on spectroscopy were also featured at the meeting.

One poster presenter demonstrated the functionality of three systems in the microbiology lab for identifying microorganisms.[5] UK-based consultant **Diane Dare** tested the capabilities of three commercially available systems: the MicrobeLynx™ by Waters Corporation, the MALDI BioTyper™ by Bruker Daltonics and the AXIMA@SARAMIS™ by Schimadzu & Anagnostec. The poster noted that "each technique has a recommended protocol for sample preparation and an associated database, together with software, for collecting the spectral patterns and interrogating the database." With little sample and prep time required, the poster stated that these systems offer "the most rapid identification methods currently available." According to the research, all three of the systems offered similar speed of analysis (1.5 hours per 100 samples). Two of the systems collect data in the range of 2 to 20,000 Da, while the other system's range was 500 to 10,000 Da. Overall, the research concluded that the three systems are suitable for rapid bacterial identification in the pharmaceutical industry.

One poster presenter demonstrated the functionality of three systems in the microbiology lab for identifying microorganisms.

[Editor's Note: The research discussed above is just but a sampling of the systems presented at the 2008 PDA microbiology conference, and does not imply an endorsement by PDA of any of the systems studied. Several of the systems examined are provided by companies that advertise in the *PDA Letter* and exhibit at PDA events, but the decision to highlight them in this article was independent of those agreements. In the next Technology Trend, PDA looks at RMMs used for air and water sampling.**]**

References

1. Poster: Evaluation, Validation, and Implementation of the Biotecon Diagnostics "Hygiene Screening System": An International Collaborative Study of a Novel Rapid Bacterial Identification Method. Brandye Michaels, PhD; Wyeth Biotech, Andover, Mass.
2. Poster: The Feasibility of Analyzing Swabs with the MicroPro. Lin Chen and Kendral Smith; Pfizer Global Research and Development, Chesterfield, Mo.; Michael Baumstein; Pfizer Global Manufacture, Kalamazoo, Mich.
3. Virus Detection for Pharmaceutical Manufacturing using TaqMan Real Time PCR. Presented by Mariela Cuadras; Applied Biosystems, Carlsbad, Calif.
4. Poster: Technical Assessment of a Bioluminescence-Based Rapid Microbiological Method (RMM) for the Detection of Microbial Contaminants in Pharmaceutical Samples. Claudio Denoya, Jennifer Reyes, and Amelia Tait-Kamradt. Pfizer Global Research; Groton, Conn.
5. Poster: Microbial Identification in the Pharmaceutical Industry: MALDI-TOF Mass Spectrographic Identification Methods. Diane Dare, Business Consultant; Cheshire, UK.

Recent Sci-Tech Discussions: Settle Plate Monitoring in Isolators; Microbiology Method Validation; and Cross Contamination Control

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.

Settle Plate Monitoring in Isolators

Is it necessary to perform settle plate monitoring during batch filling in a positive pressure isolator? Is only active air sampling enough? Settle plate monitoring will be performed during media simulation trials. Can we collate the industrial practice?

Respondent 1: [Questioner], It is not a requirement to conduct settle plate monitoring in an isolator or an other type of filling line, unless you are manufacturing product for the European market.

Questioner: Dear [Respondent 1], May I know rationale behind not performing for Non-EU market and vice versa?

Respondent 1: [Questioner], There is no defined rationale for not performing settling plates in non-EU markets. There are no non-EU regulatory requirements where this type of monitoring is required especially with the U.S. FDA. Here is an excerpt taken from the FDA Guidance Document. Annex 1 is more definitive in that is list the requirements for microbial monitoring which includes setting plates. I an not saying that you will be cited for not using settling plates for EU markets, but I know some of the EU/MHRA inspectors do expect it. See excerpt from Annex 1 Aseptic Processing General.

Active Air Monitoring

Assessing microbial quality of air should involve the use of active devices including but not limited to impaction, centrifugal and membrane (or gelatin) samplers. Each device has certain advantages and disadvantages, although all allow testing of the number of organisms per volume of air sampled.

Passive Air Monitoring (Settling Plates)

Another method is the use of passive air samplers, such as settling plates (petri dishes containing nutrient growth medium exposed to the environment). Because only microorganisms that settle onto the agar surface are detected, settling plates can be used as qualitative, or semi-quantitative air monitors.

The data generated by passive air sampling can be useful when considered in combination with results from other types of air samples.

Microbiology Method Validation

I have a question regarding submission of a Microbiology copy of an ANDA to FDA, in addition to a chemistry copy. If all methods I used for Sterility test and Bacterial Endotoxin test are per USP<75> and <85> general procedures. Is there a requirement to put the Microbiology Method Validation package in to CTD 3.2.R.P.2 as these are just "Verification" of compendial methods? Note: CTD 3.2.R.P.1 is my HPLC Method Validation package.

Respondent 1: It depends on how cocky you want or not to be. I have seen some submissions simply claiming that so…so test is compendial and they just place a copy of the official monograph page in the method description/validation sections of the ANDA for that test method.

To this approach, some U.S. FDA divisions (not all) have come back to request for some partial validation data on such compendial test methods, in accordance with the method validation guidelines.

Yet others (my preference) have duly provided a copy of the official monograph in the method description section of the ANDA and a copy of abridged validation report in the method validation section of the ANDA.

Method/system suitability and precision and/or accuracy suffice for validation of compedial test methods. But if you don't have time to pare down your full validation report and you choose to submit the full report, it won't hurt you in anyway.

Questioner: Yes, I do agree with you that eventually we are going to be asked to show suitability. That is why I plan to submit a Method Verification package in the CTD 3.2.R.3.P.2 (Microbiology Validation) right next to 3.2.R.3.P.1 (Method Validation for HPLC). Is this what everyone is doing? The verification of microbiology test method for sterility and endotoxin has no precision or accuracy issue, only sensitivity and viability of microbes.

Respondent 2: Validation/verification package for compendial methods need not be submitted in applications. You may claim that these methods are duly validated/verified and package is available for review at site.

You may submit it if the U.S. FDA requests to do so. Thanks.

Cross Contamination Control

I have a doubt regarding the cross contamination of a facility which was built years back. So posting here because of the members who are well versed with activities in GMP.

As of now I can tell you in detail the facility design. I understand that its difficult to visualize the scenario without drawing.

The facility is of multiproduct OSD facility with individual AHU for each area and the corridor which are independent. All the processing rooms have no air lock and are provided with heavy duty doors to maintain pressure differential—ve with respect to corridor.

To be clear the corridor is like an aisle where both the sides there are processing rooms with no air locks but with heavy duty doors and the processing areas maintained—ve with respect to corridor.

Granulation is of laminar flow type to avoid dust generation and having dust extractors so that sifting and milling activity can be carried out near the dust extractor. And the other areas are of turbulent type as there is no dust generation.

The corridor connecting all the processing areas is the same for entry and exit of personnel from processing areas.

Now the concern is how to prove that there is no cross contamination involved to-date?

Are there any chances of continuing with the same facility without any major modifications?

Respondent 1: Risk assessment, measurement and acceptance criteria need to be established.

Respondent 2: You need to establish residue levels in the corridor along with procedural controls over men/material/equipment flow to avoid cross contamination.

Respondent 3: I assume that the corridor is negative pressure to the rooms...in that case, unless someone has changed the rules there is no need for airlocks on each room. I also don't think that for solid dosage forms normally you need to monitor the corridor. Because it is at low pressure the corridor will be by definition cross contaminated...it is the corridor that prevents the rooms being cross contaminated.

Questioner 2: Dear Forum, Can someone throw light on the number of spikes (high counts) allowed during online particle count monitoring inside a positive pressure filling isolator during batch filling? It is understood that any spikes has to be closed with proper justification.

Questioner 1: Dear [Respondent 3],

Are you sure that the corridors need to be negative? But here, the case is that they are positive and the processing areas are negative.

As you said, if the corridor is negative then when the entry and exit is through the same corridor which is contaminated, the personnel entering into the processing area are carrying the contamination.

How do you control this?

Respondent 4: [Questioner 1],

I have seen in oral solid facility with the design you have mentioned. Also the corridor is provided with dedicated/fresh air AHU's and kept at positive pressure with respect to rooms confined the dusts in the process areas only. Regular monitoring of pressure differentials, proper man-material movement, training about do's & don'ts when moving from process rooms to corridor and if required to second room shall be done.

I know people ask this question, but most of the old facilities are like the one you mentioned.

In Oral Solid's, I have not seen a corridor at negative pressure.

Respondent 5: Dear [Questioner 1], Corridor should not be negative to the operational rooms.

Respondent 6: Dear [Questioner 1], In a solid dosage manufacturing facility, the corridor needs to be positive to the manufacturing room such that the outside environment is not contaminated.

Respondent 3: Can someone clarify this negative and positive pressure for me. I some time ago had a design for a solid dosage unit. The operational areas were positive to the corridor but the corridor was negative to the outside. The engineers advised me that this was perfectly acceptable with containment because the corridor was negative to the outside environment but cross contamination was avoided because the working areas were positive to the corridor. The corridor was considered contaminated and all rooms had their own manometer controls and warnings plus dust collecting mats on the floor.

Was this wrong?

Questioner 1: [Respondent 3], What I feel is the concept of negative pressure for the corridor is acceptable provided you have air lock where the airlock will be positive w.r.t to the processing area and corridor thus preventing cross-contamination.

Respondent 7: [Respondent 3], OSD isn't my field but from a purely logical perspective I thought your suggestion of a corridor in negative differential to the production areas sounded ok. If you wanted a higher level of cross contamination avoidance then add airlocks to each production area and for the corridor. Those persons who suggested a positive pressure central corridor would need to add an airlock into each processing area; otherwise each one would get contaminated by any activity with any other product in the corridor. Another thing would be to look at how many AHU were used and whether the air was single pass or recycled since that will also play a role. Of course if the product was highly active that would be another issue. If nobody else replies then the person asking the original question could also check out the ISPE Baseline Guide Volume 2, Oral Solid Dosage, I'm not familiar with that one but it might help with general principles (see: http://www.ispe.org/cs/cs/baseline_guides).

Regards.

Respondent 6: Hi, [Respondent 7 and Respondent 3], I think the challenge in this discussion is to address a much more complex issue than simply whether a corridor in negative differential to the production areas. Room relative pressure is part of the contamination control process that needs to be addressed in the design, construction and validation of the facilities/HVAC systems. Without fully understanding the design of the corridor, manufacturing rooms, and the air-handling systems to these areas, it is difficult to give a meaningful answer. We are talking about level 3 protections areas (Which is a "controlled" area in which specific environmental conditions are defined, controlled and monitored to prevent degradation of the product. Ref: ISPE- Pharmaceutical Engineering Guide for New and Renovated Facilities, Volume 2 Oral Solid Dosage Forms).

According to the guidance here:

1. There is no quantified (numerical) requirement for relative pressurization. The velocity and direction of airflow between spaces should be adequate to reduce counterblow of airborne particulates or vapor contaminants for spaces where airborne cross contamination is a concern.
2. In general, relative pressurization should be set up to reduce airborne particulates and vapors from passing from an open level 3 protection processing space to another incompatible level 3 protection space. Conversely, pressurization should be set up to reduce airborne particulates from passing from the outdoors, above ceilings, mechanical or similar spaces and from level m1 protection areas to level 3 protection processing spaces. Air locks or buffer zones can be used to separate production areas from adjacent common corridor/staging areas, non-controlled areas and potent drug manufacturing areas.
3. Pressured airlocks may have either positive or negative relative pressure, depending on what is best for the particular situation.

In a solid dosage form manufacturing area, the possibility of the presence of airborne particulate matter is very high, as we all know.

Respondent 8: I'd say, from an experience of auditing about 20 factories annually, that for oral solid dosage forms, about 75% of places have the central corridor positive to the tableting rooms, while 25% have it the opposite—If well controlled and routinely monitored, I'm not sure that either way has benefits over the other.

Respondent 8: Dear [Respondent 6], I find the World Health Organization Supplemental Guidelines on GMPs for HVAC systems to be much for helpful, with much more precise requirements, than the ISP document.

Questioner 1: My concern is here not the pressure differential of areas. My concern is how to prove that there is no cross contamination involved with earlier said design. Can anyone help me out?

Respondent 9: Dear [Questioner 1], you should have a positive pressure difference between clean rooms with the same grade but notice that the most critical room (e.g., Filling or rooms with Class A Laminar Flow within) should have the highest pressure value. Positive pressure difference or a minimum value established by yourselves should be enough for avoiding cross contamination.

Respondent 2: Please refer to "ISPE Baseline Guide, Volume 10, Risk APP." It's a very good read for all these cross contamination issues.

Respondent 8: Smoke studies - part of the WHO Guideline for visualization studies. With Best Regards.

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

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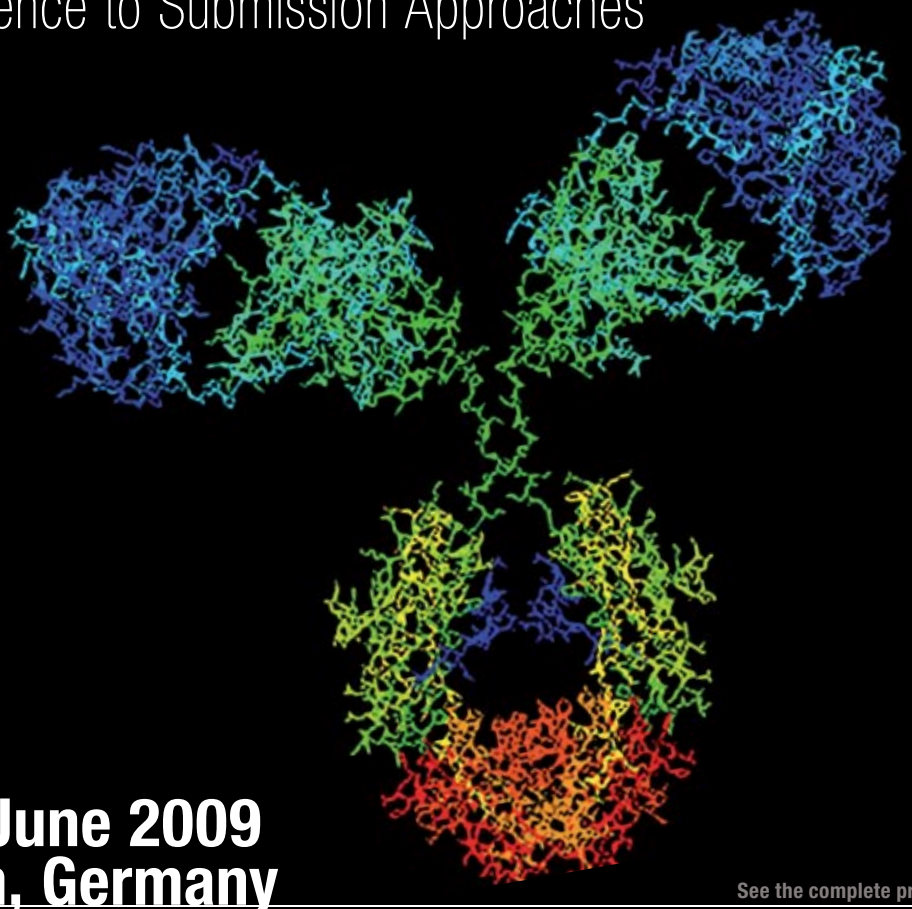

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While the principles of Quality by Design (QbD) are defined in the ICH Q8, Q9 and Q10 guidances both industry and regulatory authorities continue to grapple with interpretation and translation of the concepts into a submission framework acceptable to worldwide regulatory bodies. Practical examples showing how QbD can be utilized will help implement this important regulatory concept and enable the intended benefits. To this end, collaborative industry-based efforts have been initiated with the goal of demonstrating how QbD can be utilized for a monoclonal antibody submission. This workshop will provide a forum to review the progress from these initiatives and facilitate discussion of the output. Additional presentations will focus on key technical topics illustrating the importance of scientific understanding to QbD. A key objective for this workshop is to promote continued dialog between industry and regulators involved with both submission review and inspections. A session featuring two of the leading European regulatory authorities on QbD and MAb's will foster this dialog.

It's Time To Get Rapid, continued from cover

validate and implement the IMD-A for routine use. Therefore, conducting a comprehensive financial analysis and linking this information to other business, technical and quality benefits that the RMM may afford should permit a firm to make an appropriate decision on whether or not to proceed with an implementation plan.

Is There A Guidance On Validating A RMM?

Absolutely. In addition to TR-33, the United States and European Pharmacopoeias both have informational chapters on this subject. USP <1223> *Validation of Alternative Microbiological Methods,* and EP 5.1.6 *Alternative Methods for Control of Microbiological Quality* provide recommendations on the use of RMM validation criteria, such as accuracy, precision, specificity, limit of detection, limit of quantification, linearity, range, robustness, ruggedness and equivalence. Both of these documents show similarity to the current TR-33; however, slight differences do exist, which may make it somewhat difficult to design a validation plan that will satisfy the expectations and acceptance criteria for all three. Furthermore, there is a need to provide greater detail on the practical side of the validation process, such as the selection of an appropriate statistical model for each of the validation criteria, what to do in the event a RMM provides greater counts than the conventional method, evaluating false positives, false negatives and system noise, and the potential impact of stressed, injured and/or viable but non-culturable organisms. For these and other reasons, TR-33 is currently undergoing a substantial revision process that is due to be completed by the end of this year, and I will be presenting an overview of these changes during the PDA Annual Meeting in Las Vegas. Although the revised TR-33 will provide a more comprehensive guidance document for RMM validation and implementation strategies in the future, the industry has successfully utilized the current TR-33, USP and EP informational chapters for the qualification of many RMM systems for use in both the United States and in Europe.

Do Regulatory Authorities Encourage The Use Of RMMs And Are There Policies In Place That Make It Easy To Get A RMM Approved?

The answer to both of these questions is "yes"; however, RMM approvals may be *easier* than others depending on the regulatory agency involved, the RMM intended use, and whether or not an existing microbiology method (one that will be replaced by the RMM) is included in a new drug application or marketing authorization. Let's explore each in more detail.

Finally, both the FDA and EMEA have provided a number of regulatory approvals for the use of RMMs as alternatives to conventional microbiological testing.

There are several regulatory guidance documents that encourage the use of new microbiological technologies, including RMMs. The U.S. FDA *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing* states that other suitable microbiological tests (e.g., rapid methods) can be considered for EM, in-process control testing and finished product release testing after it has been demonstrated that these new methods are equivalent or better than conventional methods (e.g., USP). Additionally, the FDA Process Analytical Technology (PAT) initiative describes a regulatory framework that will encourage the voluntary development and implementation of innovative approaches in pharmaceutical development, manufacturing, and quality assurance. Many new technologies are available that provide information on physical, chemical, and *microbiological* characteristics of materials to improve process understanding and to measure, control and/or predict quality and performance. Furthermore, the FDA Center for Biologics Evaluation and Research has recently provided a draft Guidance for Industry entitled *Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products.* The guidance is specifically focused on growth-based methods for cellular products, and a validation approach similar to what is contained in the guidance was used by Genzyme Biosurgery to gain approval to use the bioMerieux BacT/ALERT, a growth-based RMM, for the sterility testing of cell-based products. Next, **Brenda Uratani**, PhD, Consumer Safety Officer, U.S. FDA, recently described the benefits of using a RMM during *PDA's 2nd Annual Global Conference on Pharmaceutical Microbiology.* She spoke about automating the testing process, electronic capture of test data and information creation, the ability to initiate investigations earlier as compared with conventional methods, the reduction of risk associated with microbial contamination and the use of the data as a continuum for process improvement. Finally, both the FDA and EMEA have provided a number of regulatory approvals for the use of RMMs as alternatives to conventional microbiological testing. For example, GlaxoSmithKline received FDA-approval to use the Pallchek ATP bioluminescence system for the rapid release of a non-sterile, prescription nasal spray, and more recently, Alcon Laboratories received FDA-approval for a rapid sterility test using the AES-Chemunex ScanRDI.

Regulatory agencies will generally accept a change in a manufacturing or testing process if the change has been proven to be equivalent to or better than the system currently in place. However,

the acceptance of RMMs by regulatory authorities throughout the world has been somewhat varied, and it is this variability that may be a concern when considering an implementation and regulatory strategy. For example, a single facility may manufacture a product for distribution to a number of different countries and would therefore be regulated by an equal number of independent regulatory authorities. With global regulatory harmonization unlikely in the near future, the ability to understand the requirements of multiple regulatory authorities may be necessary when considering RMMs. For the purpose of this discussion, I will primarily focus on the current policies in the U.S. and Europe.

Within the United States, PDA TR-33 and USP <1223> can serve as a jumping off point for discussions with the FDA on the validation and implementation of a RMM. There are a number of options for qualifying a RMM that will be used to support the manufacture of FDA-regulated drug product. If the RMM will be used with a new product, a firm may include the RMM in a new drug application or an abbreviated new drug application. If the RMM will be used with an existing product, and the RMM will replace a microbiology method that has been included in the product's original regulatory submission, then it may be necessary to file a post-approval change or prior-approval supplement in the relevant Chemistry, Manufacturing and Controls (CMC) sections for that product. Once a RMM has been approved, either in an NDA, ANDA or a prior-approval supplement, subsequent product filings may include the RMM in an Annual Product Report. Another option is to file a comparability protocol (CP) and manage the method change through the FDA PAT initiative.

A CP is a well-defined, detailed, written plan (and prior-approval supplement) for assessing the effect of specific CMC changes in the identity, strength, quality, purity and potency of a specific drug product as these factors relate to the safety and effectiveness of the product. The CP describes the changes that are covered under the protocol and specifies the tests and studies that will be performed, including the analytical procedures that will be used, and acceptance criteria that will be achieved to demonstrate that specified CMC changes do not adversely affect the product. Furthermore, the CP can be particularly useful for changes of a repetitive nature, such as the use of a RMM for multiple products or processes. More importantly, the use of a CP simplifies the process of reporting the change, especially when the approved CP covers subsequent CMC changes for multiple products and/or multiple

According to some industry experts, the era of the agar plate is coming to an end and the time for rapid methods is now.

BioVigilant Systems, Inc.

microbiology applications. Once the CP is approved, the experiments are performed, and if they meet the acceptance criteria provided in the CP, a special report [21 CFR 314.81(b)(3)(ii)] to the relevant application is submitted. The special report references the approved CP and includes a brief description of the RMM and its use, confirmation that the acceptance criteria have been met and the date of implementation. The special report is a very brief document, as small as one page, because there is no need to provide any data in the report. Under this strategy, any future CMC changes covered under the approved CP can be made without the need for additional approvals, and a reduced reporting category can be realized, such as a changes being effected (CBE)-30 or CBE-0. It should also be noted that CPs have been successfully used by a number of firms to implement RMMs for FDA regulated products.

For many RMMs, the FDA is now encouraging changes to be managed under the PAT model, especially if the intended change is for an in-process test, such as bioburden and purified water testing and EM. In this case, the PAT submission will be assigned to a PAT Review, Inspection and OPS Policy Development Team (PATRIOT) consisting of CMC reviewers, compliance officers and investigators. The PAT application can include the use of a CP and pre- and/or post-approval inspections. Because the most appropriate regulatory strategy (PAT, CP, prior-approval supplement, etc.) will depend on the microbiology method change, the manner in which the method will be used, and the product(s) that will be affected, it is highly recommended to discuss the proposed change with the FDA early in the implementation process. This is especially true for RMM changes that will impact in-process microbiology methods that are not included in an NDA or ANDA, because the change may actually be managed through a firm's internal change control program instead of a formal regulatory process. Finally, the FDA expects that higher counts will be recovered when using RMM technologies that are more sensitive than conventional methods.[3] In this instance, any potential changes to existing microbial specifications should be discussed when developing the RMM regulatory strategy.

Like the USP chapter <1223>, EP 5.1.6 can provide a starting point for discussions with European regulators in developing an appropriate strategy for the validation of RMMs. Although specific issues can be expected from individual member states during the registration process, the mutual recognition process does help to reduce questions and ultimately saves time and effort on the ➤

part of the applicant. However, the current European regulatory environment (for gaining RMM approval) may not be as straightforward as in the United States. Although individual member states have approved RMMs for routine use, many of the tools provided by the FDA do not exist within the EMEA. For example, there is no equivalent to the comparability protocol in Europe, and for those RMMs intended to replace existing microbiology methods that have been incorporated into marketing authorizations, the filing of multiple type variations may be required for each product, instead of being managed under a single CP. On the other hand, RMMs that are intended to replace existing methods that are not part of a regulatory dossier may manage the change internally and without the need to submit a formal regulatory submission. In either case, greater emphasis is given in Europe to equivalence testing between a RMM and the conventional test it is intended to replace. This contrasts to the situation in the United States where equivalence is not seen as such a priority due to the very different natures of new and conventional methodologies. Finally, the European PAT initiative has been taking shape over the last few years, but it still isn't as far along as the United States with respect to RMMs. Although we wait for future direction from the EMEA on how RMM PAT submissions will be handled in the future, it is obvious that the European authorities are receptive to new technologies and are open to dialogue with firms interested in RMM implementation. As a final note, discussions were held with the EMEA Quality Working Party and the ad hoc GMP inspector's group with respect to the use of RMMs for the assessment of purified water. The two groups acknowledged EP 5.1.6 and the acceptability of rapid microbial methods to replace the standard pharmacopoeial methods provided appropriate validation is performed. It was then suggested that the introduction of such methods might require specific review to ensure that the appropriate validation steps (in EP 5.1.6) have been followed and that the water continues to meet the Ph. Eur. specifications. Since, in the case of water, the validation will not be product specific, it was further suggested that a company could request the supervisory authority to carry out a specific site inspection, and the performance of such an inspection would be at the discretion of the supervisory authority and could involve a pharmaceutical assessor where necessary. Since it is expected that the water will continue to meet Ph. Eur. specification, if tested, no change to dossier requirements (variations) would be involved and therefore no regulatory impact on individual products would normally be anticipated. This would, however, depend on the level of detail in the original dossiers concerned.

Whether a firm plans on satisfying the expectations of the FDA, EMEA or another regulatory authority, it is very important to discuss the RMM qualification and implementation plans with the relevant agency early in the design phase to ensure that the best strategy is agreed upon.

What Does The Future Of Rapid Methods Look Like?

For sterile products, I envision using RMMs to support the parametric release of aseptically-filled product. That's right, parametric release. Let's put this idea into perspective.

The EMEA *Note for Guidance on Parametric Release* (CPMP/QWP/3015/99) defines parametric release as a system of release that gives assurance that the product is of the intended quality based on the information collected during the manufacturing process and on the compliance with specific GMP requirements related to parametric release. Consequently, parametric release is used

Lasers are used in the real-time detection of airborne microorganisms

as an operational alternative to routine release testing of certain, specific parameters. For terminally sterilized product, this means that a batch is released based on process data rather than on a finished product sterility test. In November 2008, the EMEA published a concept paper on the revision of the *Guideline on Parametric Release*. The problem statement is that the current guidance for parametric release does not reflect the recent regulatory development on PAT, Quality by Design and real time release. This is where the true potential for RMMs comes into play. If we are able to generate real-time and continuous microbiological monitoring data during aseptic processing, while operating in an environment that eliminates human-borne contamination, such as an isolator, we may be able to justify the elimination of the end-product sterility test because we will demonstrate (during manufacturing) that the finished product is of the intended quality with respect to microbiological control. We would, therefore, need to put in place continuous and real-time technologies for the analysis of raw materials (e.g., purified water), pre- and post-filtration bioburden and EM. Today, there exists a RMM technology that can deliver at least one of these deliverables for EM. The BioVigilant® IMD-A™ has the ability to continuously monitor manufacturing environments (i.e., conventional cleanrooms, isolators and RABS) for both viable and non-viable particles and reports the data in real-time. Amgen Quality VP **Martin Van Trieste** recently commented that the BioVigilant system represents a paradigm shift in the way we can perform EM.[4] He stated that rather than having to be reactive, the system allows firms to "look ahead of time and say, 'is there anything there that I should be concerned about and do something about before I put my product at risk?'" Additional insights into the BioVigilant® IMD-A™ will be presented during the *2009 PDA Annual Meeting* in Las Vegas, where I will share a case study on the use of the technology for real-time EM in manufacturing isolators. Furthermore, two papers detailing these studies will be published in the PDA Journal mid-year.

In closing, the implementation of RMMs represents significant progress toward the acceptance of microbiological PAT solutions for the industry, and is directly aligned with the expectations for pharmaceutical manufacturing, quality and operational excellence in the 21st century. It is time for the industry to move forward and embrace the future of microbiological methods. It really is time to get rapid!

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Quality & Regulatory Snapshot

International Pharmaceutical *Quality*

The Dialogue turns to Annex 1: Visit www.ipqpubs.com for the full issue

Bill Paulson, IPQ

The challenges of interpreting and implementing the European Union's revised GMP Annex 1 on the *Manufacture of Sterile Medicinal Products* are prompting closer scrutiny of the foundation on which the annex and other aseptic processing regulatory standards are based.

With the effective date looming for the Annex 1 revisions, cleanroom experts have been taking a hard look at how the new guidance aligns with the other regulatory standards and with the advancements in scientific understanding and the application of quality risk management (QRM).

This evaluation has important implications for the future direction of regulatory guidelines in the aseptic area as well as across the wider GMP spectrum.

Among the issues that are surfacing is how much trust manufacturers are willing to place on their own science and risk assessments when they lead to different conclusions and approaches from the Annex 1 provisions and/or the other standards. Of concern is not only the strength of a firm's process control understanding and application, but the ability of regulatory agency inspectors to make the same assessments and allow for QRM-based flexibility against the published benchmarks.

> **Also at issue in the Annex 1 discussions is the role that regulatory guidance can and should play in helping improve industry practice and mitigate risk.**

Emerging into relief is the inherent tension between prescriptive rules and the science and risk-based thrust of the quality regulatory initiatives underway in the United States and Europe, and internationally through ICH, intended to provide a more continuous improvement/technology-friendly compliance environment. The manufacturing difficulty and the stern consequences of failure increase this tension in the aseptic processing context.

Aware of where the pitfalls lie, regulators want to assure that the control requirements are clearly understood and in place. On the other hand, they are sympathetic to the need for regulatory flexibility to foster better technological solutions to the aseptic processing challenges and to allow control resources to be most effectively deployed. Industry likes the security more prescriptive guidelines give in navigating the complex shoals of aseptic processing and assuring compliance given the hefty investments involved, while wanting the freedom to apply new knowledge gained and not waste time and money on compliance for compliance's sake.

Complicating the issue for aseptic processing is that adding requirements that entail more intervention may be counterproductive in lessening the overall contamination risk. Further, specificity in stated requirements leads to confusion when there is not enough context included to understand how and where they should be applied, particularly when the vagaries of microbiology evaluations are brought into the equation. Requirement specificity may also work against the goal of harmonization.

The revisions in Annex 1 have added significance in that the EU GMPs are adopted by the Pharmaceutical Inspection Cooperation Scheme (PIC/S) and therefore will apply in member countries outside Europe that use the PIC/S GMPs, such as Australia, New Zealand and Malaysia.

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CBER Takes Lead on Validating Rapid Micro Methods

Walter Morris, PDA

It is no secret that the U.S. FDA looks favorably upon improved technologies for the manufacture and control of the products it regulates.

For sterile drugs, biotech and biologics products, the Agency's guidances point to various technologies considered to offer improved manufacture and control capabilities. Rapid Microbiology Methods (RMMs) are an array of technologies that have been mentioned in a FDA guidance, and the Center for Biologics Evaluation and Research has published the first guidance on how to validate them. While the guidance is meant for a limited product class, it serves as a template for validating RMMs.

RMMs are not just preferable; they are critical, because of the unique characteristics of cell, tissue and gene drug therapies. CBER Office of Cellular, Tissue and Gene Therapies Deputy Director **Kimberly Benton,** PhD, speaking at the *PDA's 3rd Annual Global Conference on Pharmaceutical Microbiology* last October, discussed the issues involved with these therapies that make the traditional sterility test problematic.

"The biggest challenge is," she said, "some of these products have very short shelf lives. Some of these cells will lose their activity and viability if they are biopreserved, so therefore there are a great proportion of cell therapy products that are administered in 2-to-24 hours and sometimes 48 hours after the final formulation."

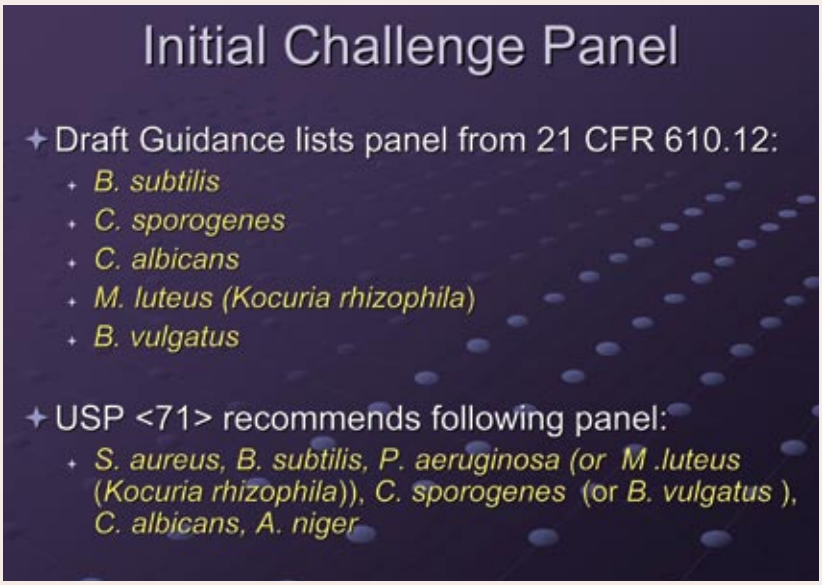
Clearly, for this product class, the traditional sterility test is not practical or useful. "They are nowhere close to getting the final results of a 14-day compendial sterility test before the product goes into a patient," said Benton. "I know that is very different from the universe that most of you deal with."

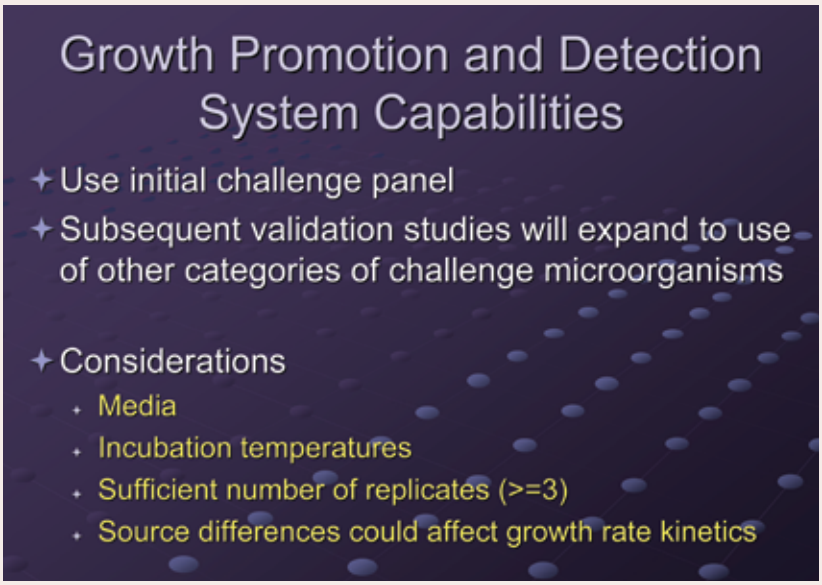
Most of the products under Benton's purview—"99.99%"—are in the investigational stage. Only one has been licensed. The guidance, therefore, will be an important tool as firms move product to the licensing stage.

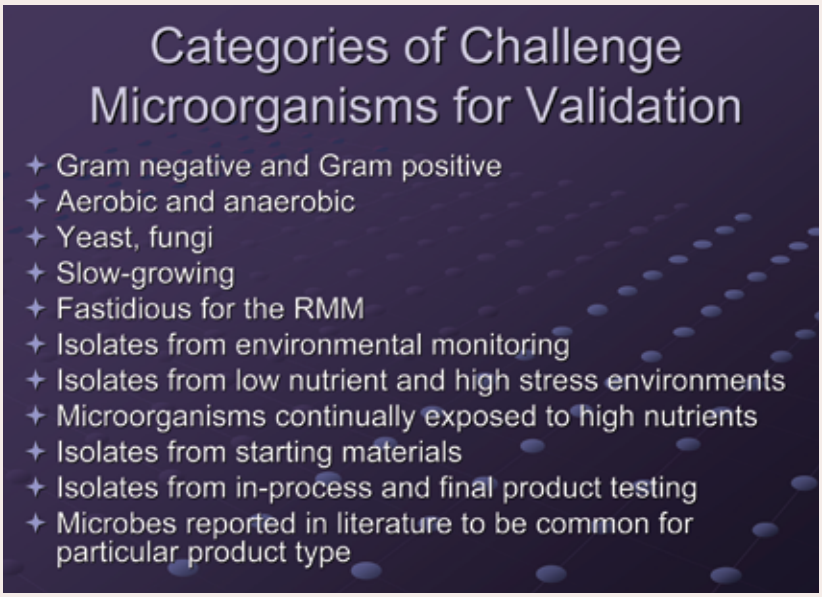
CBER released the draft guidance, *Validation of Growth Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products* in early 2008 to facilitate the use of RMMs.

Considering the various RMMs out there, Benton explained that CBER chose to focus on growth-based methods because that's where the interest of the cell and gene therapy sponsors had been. According to one of Benton's slides, *the majority of the products under IND are manufactured in academic hospital-based laboratories where clinical micro labs use automated growth-based methods.* In addition, the lab methods are *perceived by sponsors as more easily adapted for product testing.* ➤

Figures 1–3: Challenging the Growth-Based RMM from Kimberly Benton's slides







While growth-based RMMs are pretty well established vehicles in clinical labs, Benton noted that FDA "does not consider these methods to be fully validated for a broad variety of manufacturing settings." As such, the draft guidance is intended to help firms with relatively little manufacturing experience validate these methods according to the drug cGMPs.

The guidance outlines general considerations. Firms need to validate according to the potential use of the RMM, whether it be for component testing, in-process testing or testing of the drug substance or drug product.

Risk factors need to be taken into consideration when validating RMMs, including the risks associated with the cell and gene source materials. Benton noted that the starting materials include "a lot of media components" including syrup and growth factors of varying quality that can introduce risk. The "biggest source of risk" for some of these products, said Benton, is the starting cellular material themselves, e.g., material collected from tumors.

The initial challenge panel for the RMM validation recommended in the guidance comes from the sterility method outlined in 21 CFR 610.12 for biologics: *B. subtilis, C. sporogenes, C. albicans, M. luteus (Kocuria rhizophila)* and *B. vulgatus.* The guidance goes on to discuss how to ramp up the challenge in order to validate the growth promotion and detection capabilities of the RMM (see Figures 1–3).

Other areas addressed by the guidance include:

- Method comparison with 610.12
- Controls
- Validation data evaluation
- Validation under IND
- Revalidation

FDA received public feedback from companies both inside and outside the cell therapy "realm," according to Benton. Some comments asked for the guidance to be broadened to include other product types and other RMM technologies. Other comments asked for revision of 610.12 and clarification of various aspects of the guidance. The Agency is still working on finalizing the document based on feedback received at the time of press.

The most important advice companies need to remember when it comes to validating RMMs is to keep an open line of communication with the Agency. Benton stated different times during her talk that companies should discuss their plans with the appropriate review division.

NEPDA Student Chapter Meeting Introduces Students to PDA Benefits

Jessie Klein, PhD, Middlesex Community College

It's hard to believe that a year has gone by since the New England Chapter of the PDA (NEPDA) and the teachers of the Middlesex Community College Biotechnology Program committed to form the PDA's first student chapter. Since then, 38 students and three faculty members have become PDA members, Board of Directors were initiated, the Charter was approved, students and faculty attended NEPDA meetings and students presented posters at two NEPDA meetings. As the Student Chapter prepares for the Board elections, new programs are being put in place to utilize the educational and networking opportunities afforded by the PDA. The Student Chapter has begun monthly meetings where speakers will informally present the industry perspective on the subjects that the students are learning in our Biotechnology Program.

Our first guest speaker was **Louis T. Zaczkiewicz**, CQE-ASQ, the immediate past-President of the NEPDA. Louis presented "What is the PDA and What Can it Do for You?" on February 5, at the Lowell, Massachusetts campus of Middlesex Community College. (One of the frequent winter storms that we've had this year forced us to reschedule his talk from the prior week.)

Louis brought a rich history of PDA to us as one of the founders of the 20-year old New England Chapter and with his 25-year involvement with PDA. He also offers over 27 years of experience in a variety of roles in biological research, computer and U.S. FDA-regulated pharmaceutical, medical device and biotech industries. What he demonstrated over that hour surprised many of the attendees who were already somewhat familiar with PDA.

Louis presented that PDA is as an international organization of over 11,000 members dedicated to advancing pharmaceutical science. PDA publishes the *PDA Journal of Pharmaceutical Science and Technology*, Technical Reports, *International Pharmaceutical Quality* and the *PDA Letter*. PDA also has conferences worldwide, the Training and Research Institute in Bethesda, Interest Groups, Task Forces, books, an Audit Resource Center and many opportunities for volunteering.

Without logging in as a member, Louis used the search engine on the PDA website to look up information about subjects that the students suggested. Some gave minimal results, others no results. Then he logged in as a PDA member and repeated the same searches. Up came dozens of presentations on the various subjects from experts in the field. He posed a scenario: "Your boss would like you to do some research on container-closure testing, or needs some help on troubleshooting some current tests. As a PDA member you can log onto the PDA website and acquaint yourself on the subject through these presentations."

Next, he introduced the students to the Sci-Tech Discussion Forum on the website. Here they can also research pharmaceutical issues in their archives going back 13 years. He suggested that the students sign-up to receive the forum postings to their email address. He said initially that the discussions may not make much sense at first, but over a period of months they will get a crash course on various pharmaceutical issues that they will be facing at work.

Finally, he pointed out that NEPDA is planning to continue to support the Student Chapter with their initial membership costs. Additionally NEPDA is planning on putting forward a Student Scholarship program to help second-year students and the students transferring onto 4-year colleges. The details are currently being worked out within NEPDA, but the intent is to reward students who have been active in the Student Chapter and have acceptable grade point averages.

Louis' presentation showed the students the value of belonging to PDA. We look forward to continuing this monthly lecture series with NEPDA. We understand that they already have lined up four volunteers on subjects ranging from purification chromatography to analytical techniques. The schedule and information will be posted on the NEPDA website at http://pdachapters.org/newengland/. PDA members are encouraged to review the schedule and volunteer in advance by contacting **Jerry Boudreault**, the current NEPDA President, at boudreault@ddres.com.

New England Student Chapter PDA's *Who's Who*

Mariluci Bladon, PhD, Director, Biotechnology Program, Middlesex Community College, and PDA New England Student Chapter Faculty Advisor

Jerry Boudreault, President, Drug Discovery Resources, and PDA New England President

Jessie Klein, PhD, Associate Dean, Mathematics and Sciences, Middlesex Community College, and New England Student Chapter Faculty Advisor

Paul V. Patev, PhD, Professor, Biotechnology, Middlesex Community College, and PDA New England Student Chapter Faculty Advisor

Maurice Perez, Student, Middlesex Community College, and PDA New England Student Chapter President-Elect

Matthew Piasecki, Student,Middlesex Community College, and PDA New England Student Chapter President

Louis T. Zaczkiewicz, CQE-ASQ, Consultant, GXP Quality Consultants, and NEPDA Member-At-Large, NEPDA immediate past President, PDA North American Chapter Council Co-Chair and PDA Membership Advisory Board Co-Chair

PDA TOOLS FOR SUCCESS

Seven Ways to Cut Costs Without Cutting Your Lifeline

Lorraine Haataia, PhD

When the global economy is in a recession, all companies suffer, from Fortune 500s to small, family-owned businesses. And some of the weakest ones become casualties, leaving their employees without jobs, and losing customers to their competitors. During these tough times, owners, executives and managers often make decisions about jobs, resources and facilities they think they can do without and then they cut. But this isn't necessarily the best answer. The truth is, excess waste accumulates in all of these areas during prosperous times. When managers don't have to worry about the pennies, the company can quickly begin to leak dollars. And it can easily go unnoticed for months and even years.

But when the economy tightens, companies must look for innovative ways to streamline–rather than cutting what might be their lifeline. Management needs to first recognize leakage within the company, and then involve employees, suppliers and even customers to find waste-trimming opportunities. Here are seven ways your company can reduce cost and improve current business practices while strengthening the core business.

1 Have your top managers, in-house optimists and experts lead discussion groups for employees.

Employees can meet regularly to discuss articles, books or DVDs on relevant, specialized knowledge. For example, after reading a David Allen productivity book, one executive assistant came up with an idea to set up a corporate calendar with the major events at all their sites. This calendar posted on their intranet allowed for organized planning and a reduction in their travel costs by 20 percent.

2 Give employees flexibility to meet their personal goals and you'll build loyalty and engagement.

If you've never asked, you may be surprised when you learn your employees' lifestyle desires and attitudes about money. Many of them probably want more flexible work hours and breaks, instead being held accountable to work results and deadlines. If you go this route, have faith in them to help set up new pay structures. Numerous employees may take advantage of a leave-without-pay if they had the option. Compensate in proportion to incoming orders and set up pay-for-performance with cost tied to revenue.

Review your telecommuting and flex-time policies. Providing office space for all your employees is costly and often unnecessary. Consider surveying your employees for their work preferences and then set up processes and work schedules to allow more people to work remotely or from shared workstations. You can then update job descriptions, work instructions and measures to ensure that expected work results are clear to everyone.

3 Implement cost-saving green solutions.

If you're supplying coffee, disposable cups and other freebies to your employees, you may want to reconsider these expenses. Employees can bring in reusable mugs and utensils instead. Ask your employees, already passionate about the environment, to continually search for and implement cost-saving green solutions such as: installing thermostats with timers or motion sensor light switches to help reduce your utility bill, installing motion sensor faucets to help save water, or identifying vendors to purchase your waste products such as scrap metal or electronics, which can also cut back on your garbage. Green is in–go with it.

4 Regularly seek estimates from your suppliers and their competitors—you may be able to tap into a goldmine.

Your current suppliers desire to keep your business, so persist in getting at least two additional bids on all your services annually. Invite them to do an analysis for new cost-saving ideas. Befriend them as potential partners and you'll win their mental power in giving you potentially priceless ideas. This can save you a fortune over time. Even if you choose to stick with the same associates, it's always a good idea to have leverage to renegotiate rates and agreements.

5 Compartmentalize and prioritize your customers and their purchases.

Any company offering multiple products or services has some that are more profitable than others. If you haven't reconsidered your less profitable ones recently, now is the time. Analyze the segments and the cash value differences among them. Once you have this data, you can restructure your pricing or sales processes to encourage customers to behave in ways that keep your costs down, or you may even choose to discontinue some of your services. If they truly want those that are less lucrative, and you choose to continue them, adjust your prices to ensure profitability.

6 Foster trust, mental chemistry and decision-making abilities in your employees by starting a Toastmasters Club.

Many employees complain about too frequent and ineffective meetings. One solution is to start a Toastmasters Club in your company and encourage everyone to participate. It's a nonprofit organization with a proven feedback system to advance communication and leadership aptitude. Members build self-confidence, overcome fears and grow relationships. Google, Starbucks, Dell, Disney, McGraw-Hill, Microsoft and many other top organizations sponsor clubs for their employees. At less than $100 a person per year, these clubs improve participants' productivity in and out of meetings. Good communication is the most essential competency in any company with two or more people.

7 Involve employees in regularly adjusting operations to improve efficiency.

You may be surprised at the excitement when you get everyone engaged in fixing their biggest frustrations and time-wasters. If you aren't ISO 9001 certified, get a copy of this latest Quality Management System document from the International Organization for Standardization. It provides a powerful set of globally-tested principles to keep everyone focused on continually improving processes and enhancing customer satisfaction. If you don't focus on improving your work systems, they quickly become outdated, reducing efficiencies and increasing risk. Your processes drive your bottom line, day by day, toward bankruptcy or prosperity.

Employees can easily learn to recognize where time or resources are being wasted. Offer them incentives for cost-saving ideas and recognize them among their peers. Give them 10 percent back in monthly or quarterly payments, for example, against the annual savings opportunities they discover. This increases their loyalty and willingness to search for more ways to save, and the company still comes out ahead. The people you least likely expect, such as your lowest producers, might come up with the best ideas, since they're the ones who look for short cuts anyway.

Create an environment where people expect change. Once you systematize perpetual feedback from your employees, customers and suppliers, your core business will thrive regardless of economic conditions.

About the Author

Lorraine Haataia, PhD, is a consultant, corporate trainer and professional speaker who helps businesses achieve continuous improvement and growth from the inside out. As an expert in education and business process improvement, she guides clients toward improving their customers' experiences while increasing profitability. Lorraine has more than 15 years in business leadership in various industries including construction and transportation, and she earned her PhD from the University of Florida. To book Lorraine for your next event, call 904-315-8962 or visit www.DrLorraine.net.

Volunteer Spotlights

www.pda.org/spotlight

Maryellen Brown

Market Manager Life Sciences, Chisholm Corporation

Education: MBA, Bentley College; BS, Chemistry, Framingham State College

PDA Join Date: 2002

Areas of PDA Volunteerism: Event planning (2004–present); Event Registration (2004–present); Assistant to Treasurer (2004–2009); Treasurer (2009)

Professional Awards Won: 2008 New England PDA (NEPDA) President's Award for Outstanding Volunteer Service to the NEPDA

Interesting Fact about Yourself: I spend most of my free time reading, seeing movies, exercising and doing activities with my two teenagers.

Why did you join PDA and start to volunteer? I wanted to give back to an organization that provides educational events in my industry.

Of your PDA volunteer experiences, which stand out the most? Assisting with NEPDA registration has enabled me to meet and greet all the meeting attendees.

How has volunteering through PDA benefited you professionally? The events are educationally focused and provide wonderful networking opportunities.

Which member benefit do you most look forward to? Receiving the *PDA Letter* and the updated technical reports.

What would you say to somebody considering PDA membership? PDA membership is a worthwhile investment of time and resources.

Stephen Brown, PhD

Chief Technical Officer, Vivalis

Education: PhD, Microbiology, University of Kent; Postdoctoral position, Fermentation Technology, Institut Biotechnologie, ETH, Zurich, Switzerland

PDA Join Date: 2001

Areas of PDA Volunteerism: 2009 Biopharmaceutical Development and Manufacturing Conference (Co-Chair); Europe Biotech Interest Group sub-group facility and process (Group Leader); Single Use Systems Technical Report Task Force (member)

Interesting Fact about Yourself:

Originally from the UK, I moved to France 25 years ago so these days I think of myself as European. I've worked for a company in the UK and three different companies in France involved with biologics pharmaceutical development, gene therapy, cell therapy, animal vaccines and new vaccines. My wife and I enjoy living on the west coast of France and have three children. They were all born in France and are at different stages of education between the lycée in France and university in the UK.

Why did you join PDA and start to volunteer? To stay aware of the latest developments in regulatory affairs and science and technology.

Of your PDA volunteer experiences, which stand out the most? Conference organization and task force membership because they're interesting and enable you to meet many different people with varying experiences from all over the world.

How has volunteering through PDA benefited you professionally? It's been an enormous help to my understanding of the regulatory and technical issues surrounding biopharmaceutical product development and I now have a network of many contacts who are always willing to help.

Which member benefit do you most look forward to? The monthly newsletter updates. One particularly useful benefit is access to the archive of technical presentations.

Which PDA event/training course is your favorite? That's difficult because there are several. However, one I really enjoy is reading and contributing to the PDA Sci-Tech Web forum–it helps you keep up-to-date on many issues and provides a forum where you can express your opinions on hot topics!

What would you say to somebody considering PDA membership? Don't hesitate. You have everything to gain in terms of professional development and meeting interesting people and colleagues and the opportunities for career and personal development are significant.

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.

Asia-Pacific

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Metro
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Please Welcome the Following Industry

Fadia Alkhalil, SGS life Science

Brad Arnold, Hollister-Stier Contract Manufacturing

Josette Augustin, AMAG Pharmaceuticals

Dupleix Awah, Lantheus Medical Imaging

Keith Baechle, ACH Foam Technologies

Anthony Bantug, Baxter Healthcare

Pierre Barkman, UCB Pharma

Lisa Barsuli, Baxter Healthcare

Michael Birck, Alkermes

Nadine Bouchard, Theratechnologies

Joseph Bradley, Biocorp

Phillips Bradley, Gen-Probe

Chayla Brown, Sanofi Pasteur

Paul Burke, Merck

Matt Cahill, Accugenix

John Caldwell, Bayer Healthcare

Brian Callahan, ISNetworld

Nicole Carvalho, Millennium Pharmaceuticals

Patricia Cash, MedImmune

Roberto Cassaniti, GlaxoSmithKline

Angelo Celli, Facta Pharmaceuticals

Tarun Chugh, Baxter Healthcare

Kathy Coleman, Nosco

Edward Conard, Imclone Systems

Erica Connolly, Infinity Pharmaceuticals

Andrew Cook, Cephalon

Birgitta Danell, Biovitrum

Loretta De Souza, Cangene

Thomas Dee, TBS Technologies

Jo Beth DeFreitas, Genentech

Frank Devlin, CVS Caremark

Helen Dickinson, APP Pharmaceuticals

Anette Drojdahl, Dansk Teknologisk Institut

Philipp Eberhardt, NNE Pharmaplan

Duane Eckelman, Schering-Plough

Michael English, Merck

Arthur Fiocco, Hospira

Ingrid Freeland, Astellas

Krista Fresenborg, Eli Lilly

Rikki Frizell, Boehringer Ingelheim

Markus Gantert, F. Hoffmann - La Roche

Erick Garcia, Baxter Healthcare

Paul Gauthier, Shire HGT

Robert Gay, Amgen

Adolfo Gomez, Tecnofarma

William Greenhut, Wyeth Biotech

Steven Grieve, Pfizer CentreSource

Anthony Guacci, Par Pharmaceuticals

Marc Habib, SQA Services

Cushing Hamlen, Medtronic

Betty Hannoun, Merck

Kim Hanock, Ferris State University

Rune Leeth Hansen, Alpharma

Diane Hardy, Regeneron Pharmaceuticals

Christine Hartline, Teva Pharmaceuticals

Kalli Hatziaghelidou, Demo

Rexford Hayes, Immunogen

Jennifer Headding, Boehringer Ingelheim

Catharina Hendrickx, Pfizer

Lawrence Herbst, Catalent Pharma Solutions

Midori Hironaka, Novartis

Derek Hodson, Foamtec International

Veronica Hunter, Dyax

Maria Ingevaldsson, Lakemedelsverket

Steven Ito, Astellas

Russell Jacob, Shire HGT

Ryan Jarvis, Sensitech

Rasmus Jespersen, Novo Nordisk

Jana Joericke, IDT Biologika

David Johnson, AstraZeneca

Claude Jolicoeur, McKesson

Kare Kallmyr, Norconsult

Denise Kemp, Regeneron

Walter Kibbe, GlaxoSmithKline

John Kirchner, JK Lifesciences

Steven Kramer, Pulmatrix

Brian Lasher, Covidien

Adrien Lehideux, Coldpack

Jee Look, Intercell

Rick Lu, Sartorius Stedim Biotech

Ian Luginbuhl, Sanofi Pasteur

James Mann, Novartis

Fernando Marcellan, Pall Life Scieces

Andrew Marshall, Honeyman Group

LeeAnne Masiowski, Cangene

Christofer Matney, Indianapolis Airport Authority

Sean McGowan, Shire HGT

John McMican, JHP Pharmaceuticals

Antony Meaden, Novartis

Leaders to the PDA Community

Heike Merget-Millitzer, Cilag

Michael Milligan, Genentech

Melissa Morandi, Quality Consultant

Monte Moss, Hollister-Stier Laboratories

Karen Mullin, Meridian BioGroup

Minh Nguyen, Gish Biomedical

Courtney Noah, Pall Corporation

Jamie Noto, Imclone Systems

Liz Nouaime, Endo Pharmaceuticals

Stephen Omlor, Ovation Pharmaceuticals

Rachel Ozer, Ottawa Health Research Institute

Betsy Parrott, Baxter Pharmaceutical Solutions

Janet Perez-Brown, Bristol-Myers Squibb

Indira Persaud, Biogen Idec

Helle Teglgaard Petersen, Alpharma

Carolyn Rasmussen, Pharmaceutical Trade Services

Ed Reeher, Performance Validation

Linda Rendon, Hollister-Stier Laboratories

Robert Resker, The Continuum Alliance

Marie Reynolds, Pfizer

Tomas Risberg, Octapharma

Luis Rodriguez, Bayer Healthcare

David Rohrbach, Eagle Pharmaceuticals

Jerry Rose, CVS Pharmacy

Shaun Ross, Commissioning Agents

David Rudd, Cardinal Health

Annie Rudkin, Amgen

Djerki Ruzica, Genentech

Jessica Saggers, West Pharmaceutical Services

John Eric Salvador, Genentech

Anup Sampat, Iroko Pharmaceuticals

Philip Schneider, LexaMed

Neil Schwarzwalder, Eli Lilly

Jeff Silkstone, Charter Medical

Peter Simms, Grifols Biologicals

Gurminder Singh, Sanofi Pasteur

Kevin Song, B. Braun Medical

Morten Stenkilde, Novo Nordisk

Paul Sugiyama, Exelixis

Ernie Swanson, Genentech

May Tang, Sanofi Pasteur

Luciano Tavares, NNE Pharmaplan

Joe Tenhagen, Nosco

Romit Thakore, Shire

Arun Tholudur, Amgen

Angela Thomas, Eli Lilly

Rodney Thompson, BioPharm Process Associates

Jamie Tsung, Shire HGT

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Ernst van Bockxmeer, Schering Plough

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Jason Vorhees, Genentech

Kristi Vrkljan, ARCA biopharma

Greg Walker, Performance Validation

Renee Wallace, GlakoSmithKline

Chunxiang Wang, Lauradvice

Michael Weber, Millipore

Fred Weber, Sterility Assurance Labs

Douglas Wettergren, Envirotainer

Jakob Wiborg, Novo Nordisk

Craig Winstanley, Novartis

Sabrina Wolff, IDT Biologika

Florence Wu, Aemtek

Philip Wyche, Shire HGT

Ed Yaworski, Tekmira Pharmaceuticals

Dag Yemenu, ISNetworld

Hiroshi Yoshikawa, Takeda

Carlos Yuraszeck, Celegene

Manuel Zahn, 3R Pharma Consulting

Rana Zoheir, Egypt Otsuka Pharmaceuticals

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

Secure Your Supply Chain

Shanghai, China • June 15–19 • www.pda.org/asiapacific

Program Co-chairs Steven Wolfgang, U.S. FDA and Janeen Skutnik, Pfizer

High quality, safe and effective drug products depend upon a consistent supply of high quality ingredients and starting materials. A multitude of risk factors can potentially affect ingredient quality and thus warrant careful consideration when approving suppliers and making accept/reject decisions on purchased articles. The complexity of international drug product sourcing, manufacturing and distribution strategies is bringing users and suppliers of ingredients and starting materials together to assess and manage quality risks. As we are learning from recent experiences of users of ingredients and starting materials, risks are not readily apparent or safely mitigated simply by reviewing a specification in a catalog, a certificate of analysis or on the basis of limited testing. Risk mitigation approaches involve building robust quality systems and relationships with suppliers such that there is a focus on quality within the entire supply chain.

Despite the diversity in locations and sourcing strategies, there is a surge in global cooperation and efforts toward harmonization of GMPs and GDPs (good distribution practices) and controls pertaining to the supply chain among members of industry and the regulatory agencies. All seem to agree that working relationships and openness among users and suppliers will strengthen the quality of manufacturing and distribution practices throughout the life cycle of an ingredient. Understanding and securing the entire ingredient manufacturing and distribution chain can increase confidence in quality of ingredients and starting materials, and ultimately helps ensure the quality and safety of medicines for our patients.

On behalf of the Program Planning Committee, we would like to invite you to attend the *2009PDA/FDA Asia-Pacific Pharmaceutical Ingredient Supply Chain Conference*, which includes an exhibition and training courses. The program will bring attendees up-to-date with the most recent activities among stakeholders from North America, Europe and Asia to identify and implement best practices in the ingredient supply chain. Leaders of the movement from regulatory agencies, industry, health organizations, and trade associations will share their personal and collective observations and ideas during eight sessions covering:

- Challenges in ensuring the quality and integrity of pharmaceutical ingredients
- Regulations and guidance on GMPs and GDPs
- The role of quality systems in supply chain operations
- Industry practices from the perspectives of suppliers and users of starting materials and ingredients including API manufacturers, excipient manufacturers, drug product manufacturers and distributors of these materials
- Opportunities for global cooperation, collaboration and harmonization

Please join us at the PDA/FDA Asia Pacific Pharmaceutical Ingredient Supply Chain Conference and take advantage of this opportunity to participate in the global initiative to ensure the integrity of the Pharmaceutical Ingredient Supply Chain. We encourage all members of the pharmaceutical ingredient and ingredient starting material supply chain to attend, to learn about today's global regulatory environment as it relates to the harmonization and implementation of modern systems for assuring and maintaining pharmaceutical quality. You won't find this level of direct information exchange with members of industry and regulatory agencies leading the movement to promote ingredient quality and security at any other conference!

Be a Part of the Discussion at the Cell Substrate Workshop

Bethesda, Md. • July 29–30 • www.pda.org/cellsubstrate

Workshop Committee Co-chairs Kathryn King, PhD, U.S. FDA and Michael Wiebe, PhD, Quantum Consulting

As a result of technological advances within the industry, we are now able to produce recombinant proteins for human-use more efficiently and in a wider variety of cell substrates than ever before. Alongside the benefits derived from these advances come new challenges in ensuring biopharmaceutical product safety. The aim of this workshop is to provide an interactive forum in which these issues can be brought forth in the form of case studies and addressed by members of industry and regulatory authorities during an open discussion.

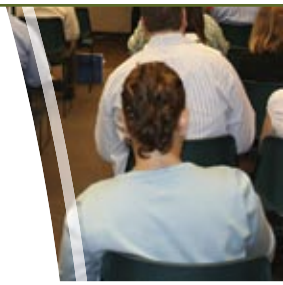
The *PDA Cell Substrate Workshop* will be divided into three focus areas: cell line engineering and new cell substrates; raw materials impacting cell substrates; and virus testing of cell banks and unprocessed bulk. The opening session will include a keynote address by **John Petricciani,** MD, who will set the stage for the meeting by providing an historical overview of the use of cell substrates for biopharmaceutical production.

The session on **New Cell Lines and Cell Line Engineering** will begin with a focus on cell line engineering strategies that have been employed to boost recombinant protein production and the requisite safety testing required. It will then branch out to alternative production systems for therapeutic protein production including human, insect and avian cell lines and will conclude with an U.S. regulator's perspective on appropriate safety testing for these new and engineered cell lines.

The **Raw Materials** session will focus on raw materials as a potential source of adventitious agents. Speakers will address strategies employed to mitigate the risk of adventitious agent contamination of raw materials, as well as U.S. regulatory expectations with regard to raw materials.

Prior to a wrap-up session pertaining to the entire meeting, the second day will begin with a **Virus Testing session**. This session will provide new strategies for viral testing of cell lines. Cases of detection of viral contaminants will be reported and the experience of industry with the ICH Q5A based approach of cell line testing will be summarized on the basis of a survey. Regulatory expectations on validation/qualification of virus assays will be discussed from the standpoint of the German Paul Ehrlich Institut.

This session will be followed up with a synthesis session in the form of an open discussion. From the synthesis session we hope to identify issues that remain unresolved and should be addressed further and determine in which areas consensus may be reached. We hope that you will be able to join us to participate in this upcoming workshop July 29–30 in Bethesda!



Workshop to Focus on Gaps in Combo Products Framework

Washington, D.C. • September 16–17 • www.pda.org/comboproducts

Workshop Chair Michael Gross, PhD, Chimera Consulting

For those with an interest in the regulation of combination products, I invite you to join us in Washington, D.C. on September 16 and 17 immediately following the close of the PDA/FDA Joint Regulatory Conference for PDA's first conference on combination products. The meeting should be of interest to individuals at all levels who are engaged in development, manufacture and post-marketing compliance of combination products. This will be a different kind of combination products conference. Many past conferences organized by various organizations have focused on explaining existing regulatory frameworks.

This conference will focus on the gaps in the regulatory framework and how companies that develop and manufacture combination products are actually managing difficult regulatory problems in the absence of defined regulations and guidance. The meeting will cover many case studies on the management of difficult combination product issues.

It has been almost twenty years since the U.S. FDA officially recognized combination products as a distinct medical product category. Following the Safe Medical Device Act of 1990, FDA assigned responsibility for combination product jurisdictional issues to a high-level office in the FDA Commissioner's Office, the FDA Ombudsman. Following the 2004 Medical Device User Fee and Modernization Act, focus on combination product issues strengthened and broadened through the establishment of an office focused solely on combination product issues in FDA's Office of Combination Products (OCP). Since the establishment of OCP there has been progress in the regulation of combination products the muddy waters have been clearing. However, there is still much to be done and many important regulatory problems still need clarification.

Several years ago FDA began to address the applications and safety reporting issues by publishing for comment two concept papers. In 2004, the quality system issue was initially addressed through the publication for comment of a draft guidance on *Current Good Manufacturing Practice for Combination Products*. No further regulation or guidance on these topics has been officially released, although the imminent publication of proposed regulations on combination product safety reports and quality systems is rumored. Other than discussing each issue on a case-by-case basis with agency reviewers, there is nothing else available on how to reliably manage these and other important gaps in the regulatory framework. One solution to this is to learn what others are doing.

The opening session will include presentations on the status of regulation and guidance development activities within FDA. During the conference, there will be adequate time for discussions and networking; a networking luncheon is planned that will allow participants to sit with others and collaborate on common interests and problems.

The conference will be an opportunity to fully understand the status of combination product regulations and where gaps exist in the regulatory framework. It will provide a unique opportunity to learn how some companies manage regulatory gaps in these areas. The workshop will emphasize case studies and presentations from companies developing combination products that represent model approaches to problem solving. It will provide a venue for industry and regulatory health authority experts to discuss how to manage difficult combination product regulatory issues in an evolving regulatory environment. It will be an opportunity for face-to-face dialogue on these issues and will provide industry professionals an invaluable venue for direct information exchange with their colleagues and policy makers.

I hope you will be able to join us at the 2009 Combination Products Conference and take advantage of this unique opportunity to interact on important combination product issues and hot topics with your colleagues and regulatory health authorities. For more information on the 2009 Combination Products Conference, please visit www.pda.org/comboproducts. I hope to see you there.

5 key areas in most need of regulation and/or guidance were recently identified in an industry survey:

1. **Properly designing clinical studies programs for the efficient development of a variety of combination product types**
2. **Structuring the content and format of applications for a variety of combination product types**
3. **Properly reporting various kinds of manufacturing and design changes to a variety application structures for a variety of combination product types**
4. **Properly filing safety reports for different types of combination products**
5. **Structuring quality systems for different types combination products**

Connecting Microbiology and Manufacturing

Bethesda, Md. • October 5–8 • www.pda.org/microbiology2009

Program Co-chairs Ed Balkovic, PhD, Genzyme and Bryan Riley, PhD, U.S. FDA

On behalf of the program planning committee, we would like to invite you to attend the *4th Annual Global Conference on Pharmaceutical Microbiology: Bringing Microbiology to the Manufacturing Floor*. This conference has become a tremendous opportunity to network with fellow microbiologists, experts in all areas of pharma micro, key vendors of micro testing equipment and supplies and worldwide regulatory/compliance professionals.

The conference will commence with a keynote address entitled "Pharmaceutical Microbiology – The Move from the Laboratory to the Manufacturing Floor." The scientific sessions that follow will include case studies describing the solutions to challenging pharmaceutical microbiology issues. Sessions are being planned to discuss topics, such as:

- Advances in aseptic processing
- Quality by design
- Biofilm development
- Advances in endotoxin testing
- Manufacturing contamination control
- Impact of environmental monitoring on manufacturing
- Linking risk management with economics
- Rapid methods in microbial detection
- Non-culturable organisms
- New sterilization techniques
- Reviewing global compendial topics
- New PDA technical reports

These sessions should help all of us design and implement plans to make microbiological testing results more relevant to operations as they occur on the manufacturing floor. A regulatory roundtable is also being planned for the meeting.

The conference will also include numerous opportunities to network with your fellow microbiologists. Luncheons on the first two days will provide a relaxed opportunity to discuss the issues raised during the day's presentations. Morning and afternoon breaks and a reception on Monday evening will allow time for visiting with vendors and fellow attendees. Poster sessions will also offer the chance for in depth discussion with the presenters.

Scientific abstracts for presentation at this year's meeting are still being accepted until April 30.

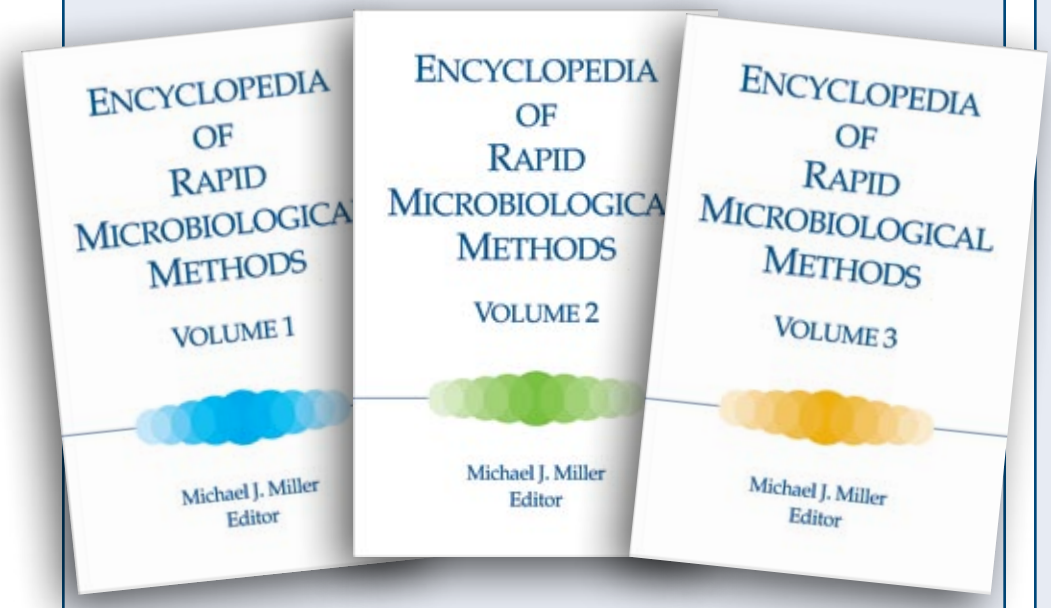
For meeting and abstract information, to submit an abstract and to register, visit www.pda.org/microbiology2009.

Recommended Reading

Encyclopedia of Rapid Microbiological Methods

Michael J. Miller, PhD, Ed.

Volume I **Volume II** **Volume III**



To order this book and more, visit www.pda.org/bookstore

Training Courses Follow Microbiology Conference!

Be sure not to miss a chance to attend a training course following the microbiology conference. On October 8th the PDA Training and Research Institute will hold three courses focused on Microbiology. Topics covered in these courses include methods and regulatory expectations for aseptic and non-sterile manufacturing, microbiological problems associated with water sources, and microbiological issues in non-sterile manufacturing.

- **Environmental Monitoring**
  October 8, 2009
- **Microbiology of Water in a cGMP Environment**
  October 8, 2009
- **Microbiological Issues in Non-Sterile Manufacturing**
  October 8, 2009

Sterilization Conference Offered in Europe and United States

New Jersey and San Juan • May, November • www.pda.org/sterlization2009

Program Chair Jim Agalloco, Agalloco and Associates

I am pleased to tell you that PDA is offering a conference on sterilization technology in different locations around the world in 2009. Knowing that travel budgets for many companies are tight, PDA and specific PDA chapters are bringing the knowledge and experience of subject matter experts to you to help minimize travel expenses and save time spent away from the office.

The next *Sterilization Technology Today and Tomorrow* conferences will be held May 14–15 in East Brunswick, New Jersey; and November 18–19 in San Juan, Puerto Rico.

These conferences will give you the opportunity to explore recently improved methods and technologies—as well as those in development for future use—for the sterilization of materials, components and finished pharmaceutical/biopharmaceutical products. The agenda will include sessions covering industry best practices developed with input from global PDA members, industry experts and regulators. Our goal is to present the most advanced approaches to sterilization in these sessions.

You will **hear directly from the experts who wrote sterilization guidance documents** and industry speakers from leading bio/pharmaceutical companies such as **Schering-Plough, Baxter, Millipore** and many more.

For more details and to register, visit www.pda.org/sterilization2009. I hope to see you and your colleagues at these events in 2009.

Specific session topics include:

- **Chlorine Dioxide: An Alternative Agent**
  Mark Czarneski, Director, Technology, *ClorDiSys Solutions, Inc.*
- **PDA Technical Report No. 26 (2008 Revision) - Increasing Confidence in the Bacterial Retention and Integrity Testing of Sterilizing Grade Filters**
  Maurice Phelan, Director, Global Compliance Services and Regulatory Affairs, *Millipore*
- **Biological Indicators: Direct Inoculation Versus Spore Strips and Ampoules**
  Jeanne Moldenhauer, Vice President, *Excellent Pharma*
- **USP Activities in Sterilization and Sterility Assurance**
  Scott Sutton, Senior Director, *Vectech Pharmaceutical Consultants, Inc.*
- **Sterilization/Sanitation/Disinfection/Decontamination: Making the Distinction**
  Art Vellutato, Vice President, Technical Support Operations, *Veltek Associates, Inc.*
- **Radiation Sterilization for Pharmaceuticals: the VDmax Method**
  John Kowalski, Senior Consultant, *Sterigenics*

New Developments in the Field of Visual Inspections Unveiled

Bethesda, Md. • October 19–20 • www.pda.org/visual2009

Program Co-chairs John Shabushnig, PhD, Pfizer and Markus Lankers, PhD, rap.ID GmbH

Visual inspection continues to be an important element of the manufacturing process and the quality assurance of injectable products. Product inspection provides necessary information for lot release and coupled with defect identification contributes to a strategy of continuous process improvement. Since 2000, PDA has organized the Visual Inspection Forum to discuss new technical and regulatory developments in this field. It has grown into the leading event for those working in visual inspection. This meeting alternates between the United States and Europe. The meeting will provide a forum to present and discuss new developments in the field of visual inspection, including contributions to a basic understanding of the sampling and inspection process, practical aspects of manual and automated methods, and the regulatory and compendial requirements that govern them.

This is an excellent opportunity to learn more about visual inspection and to discuss inspection challenges with the experts. A further goal of this conference is to build a network of experts and interested professionals working in this important and specialized field. For this purpose, we have scheduled time for both formal panel and informal discussion.

As in past years, the meeting will feature an exhibition where attendees can see the latest in commercial inspection hardware and discuss production needs with key suppliers of inspection systems and services. In addition, the vendors are being given the opportunity to give a short overview on their latest developments during a special session within the conference.

We are also pleased to add again an optional two-day training course offered through PDA's Training and Research Institute (TRI). This course covers the basics of visual inspection, establishing and managing a visual inspection program, and qualification and validation of inspection processes as applied to injectable products. It will be a combination of lecture/discussion and hands-on laboratory exercises used to develop and practice practical inspection skills. The skills developed through this course may be applied to both manual human inspection and automated machine inspection. This course will be held immediately following the Visual Inspection Forum on October 21–22 at PDA's TRI facility in Bethesda, Md.

For more information on the *2009 PDA Visual Inspection* Forum and related TRI course, visit www.pda.org/visual2009. We look forward to seeing you at this exciting and informative meeting.

Faces and Places

PQRI POPD Working Group Meeting at PDA HQ, March 18

1. James Castner
   Bristol-Meyers Squibb
2. Frank Holcomb, Jr., PhD
   U.S. FDA
3. Art Shaw
   Pfizer
4. Mike Ruberto, PhD
   Material Needs Consulting
5. Diane Paskiet
   West Analytical Services
6. Steve Beck
   GlaxoSmithKline
7. William Beierschmitt
   Pfizer
8. Desmond Hunt, PhD
   USP
9. Thomas Feinberg
   Catalent Pharma Solutions
10. Daniel Norwood
    Boehringer Ingelhgeim
11. Thomas Egert, PhD
    Boehringer Ingelheim
12. Douglas Ball
    Pfizer

All Photos & Design: James Austin Spangle, PDA

NEW this year! Immediately following the conference, PDA will host the *PDA Combination Products Workshop*.

Visit *www.pda.org/comboproducts* for more information.

2009 PDA/FDA Joint Regulatory Conference

Securing the Future of Medical Product Quality: A 2020 Vision

September 14-18, 2009
Washington, D.C.

Conference	September 14-16
Exhibition	September 14-15
Courses	September 17-18

www.pda.org/pdafda2009

The *PDA/FDA Joint Regulatory Conference* offers the unique opportunity for you to join FDA representatives and industry experts in face-to-face dialogues. Each year, FDA speakers provide updates on the current state of initiatives impacting the development of global regulatory strategies; while industry professionals from some of today's leading pharmaceutical companies present case studies on how they employ global strategies in their daily processes.

Hear directly from FDA experts and representatives of global regulatory authorities, and take home best practices for compliance. You won't find this level of direct information exchange with FDA and other global regulators at any other conference!

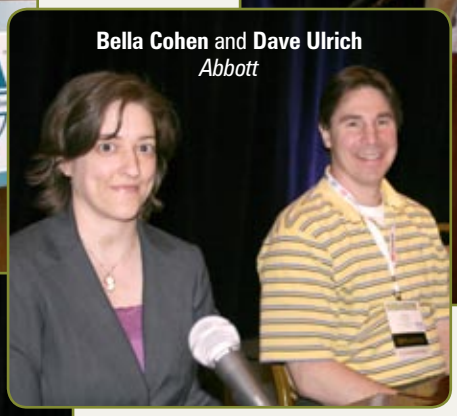
PDA is also offering an exhibition during the conference, and the PDA Training and Research Institute (PDA TRI) will host courses immediately following the conference.

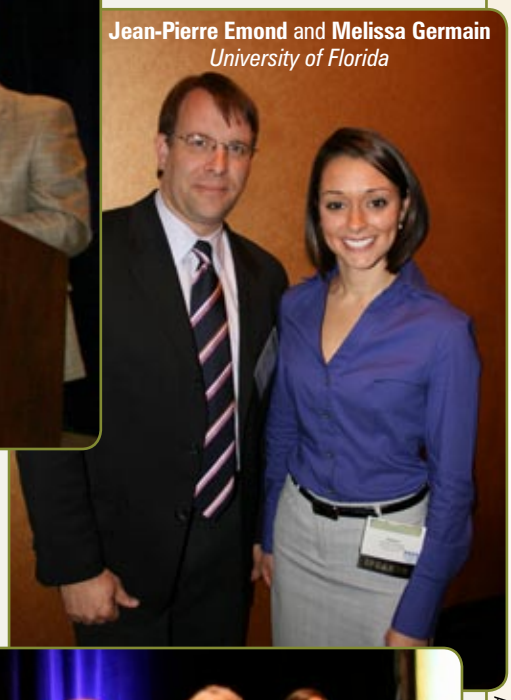
Faces and Places

PDA 2009 Pharmaceutical Cold Chain Management Conference
March 23–24, Bethesda, MD

Rafik Bishara, PhD
PDA


Ed Smith, PhD
Packaging Science Resources


Bella Cohen and **Dave Ulrich**
Abbott


Jean-Pierre Emond and **Melissa Germain**
University of Florida


Zahbea Saund
Amgen

(l-r) Dave Ray, Sensitech; Doug Dawson, Dawson Logistics; Umit Kartoglu, MD, WHO; Rafik Bishara, PhD, PDA; Gary Hutchinson, Amgen

Q&A One of the great benefits of attending PDA programs and meetings is the opportunity to discuss the most pressing topics of the day with renowned industry professionals in Q&A sessions.

All Photos & Design: James Austin Spangle, PDA

Regulatory Compliance

It's critical to keep your ducks in a row

Visit us at the 2009 PDA Annual Meeting in Las Vegas, April 20–21, 2009—Booth #812

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Selecting the Right Rapid Microbial Method for Your Application

Jeanne Moldenhauer, Excellent Pharma Consulting

Selecting, implementing, and validating rapid microbial methods (RMMs) are very valuable endeavors, but are not simple.

As a potential user, it is difficult to talk to numerous vendors and attempt to understand all of the limitations associated with each system. In addition to the difficulties in understanding limitations, another concern is how easy or difficult it is to actually use the method. It can look like a simplistic test method when seen on a video or in a presentation, but in reality it may be more difficult to convert to an isolator method, the steps are rate limiting by the time intervals allowed between steps, it may be hard to learn how to do the method (as indicated by a long time required to learn how to properly perform the method), and so forth.

When you have the opportunity to actually use the system and have a hands-on opportunity to try out the methods, there is a great deal more that you can learn about the system. For example, you might find that the system isn't compatible with your testing facility, the time to use the method is longer than the existing method, it isn't easy to use, the reagents use times are too short and other limitations.

While you might find it feasible to obtain several of these different instruments for evaluation at your site, most don't have the resources to purchase numerous RMMs to evaluate them. Many of the vendors will allow you to "try-out" a system at your site, but they tend to have a significant cost associated with the option. Depending on the system, it may be in the range of $5,000 to $10,000 a month.

Another concern is whether you have a good understanding of the systems that are available that may meet your needs for a rapid method. In reality, it is difficult to keep up with all of the systems that are available and whether they are or are not appropriate for your intended use.

TRI has developed an introductory course on RMMs to aid you in the selection, validation and implementation of these systems. This is a week-long, hands-on course that provides the opportunity to evaluate several Rapid Microbiological Systems in a laboratory-based environment. On the first day, there is an overview of the various systems available, regulatory perspectives on rapid methods (both reviewers and compliance), compendial expectations, and the experiences of real life users of rapid methods. For the remainder of the course, each day starts with an overview of the technology involved in the three systems to be evaluated for the day. The class is broken down into three groups, which rotate through each of the three labs during the day. For each lab session, the group has the opportunity to run the system and see first hand how the method works, what's involved in doing the test, and how to evaluate the data. By the end of each day, each small group has seen three systems, resulting in first hand knowledge of nine units by the end of the week. The last day, each group assesses the strengths and weakness of each system (including what they learned from these systems). After a suitable time, the groups come together and discuss the findings from the various groups for each system. As a result, attendees have the opportunities to benefit from the insight of various class members as well as with their "hands-on" experience.

In one short week, attendees get information that could cost several thousands of dollars more to obtain, supplemented by the insight of the others attending their classes.

Rapid Microbiological Methods is scheduled for August 3–7, 2009 at PDA's Training and Research Institute in Bethesda, Md. For more information please visit www.pdatraining.org/rmm.

PDA Training and Research Institute (TRI)
photos and graphics, James Austin Spangle, PDA

Recent Sci-Tech Discussions: Training From a GMP Perspective

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.

I have a question regarding training in GMP perspective: If I have made an SOP, which is checked by one of my colleagues and approved by my Head of Department (HOD):

A. Who can give training in that SOP, any one of three who signed the SOP?

B. If I give training, does my colleague who is signed under "checked by" & HOD needs to be included in training of that SOP?

C. If I have given training on that SOP to 15 people from different departments, can these 15 people further give training to other people in there respective departments irrespective of originating department of SOP?

D. Can self-reading and understanding a SOP be consider as training?

If yes, who should be put as "trained by" in such cases?

Your inputs are needed. Thanks.

Respondent 1: Dear [Questioner],

Items A and B

The persons who have signed the document may actually not be suitable for conducting the training. For example, in some companies SOP's are approved by QA, but they may not be experts on the subject matter of the SOP. Their signature is an acknowledgment that the SOP is constructed correctly and is clear and in compliance with company policy…not that the content is accurate. Under the same consideration, the signees may not always require training in the specific SOP.

Item C

The passing on of training is certainly acceptable. A multinational company in twenty countries does not send one person around to each site. However, I believe that you need an SOP to cover "qualifying" trainers.

Item D

I personally feel very strongly about this (there is an article coming out shortly on training in the Journal of GXP). I do not believe that under most circumstances a first edition of an SOP can be on the basis of read and understood. My experience in auditing companies is almost 100% correlation between the percentage of read and understood SOP's and the number of compliance issues the company has.

What I do accept is read and understood for a new edition, provided that the company follows the practice of having a clear statement as "reasons for change."

An additional point: Is training on an SOP complete if there is no test or proof. Readers might like to tell me what is the difference between read/understood signature and "sat here listening for the last 30 minutes, didn't understand much and anyway I was SMS'ing my wife"/ signature.

Finally, I also believe that trainers should themselves be trained how to carry out training. There are certain skills that can be taught and should be.

Respondent 2: Dear [Questioner], There are two aspects with respect to implementation of SOP's:

1. Reading the SOP, where it is not considered as training. In this case there will be one document which says the respective SOP is "read and understood." It is just like when a new employee joins, we will give the relevant SOP's as a part of induction and he/she will be writing in the induction report indicating so and so SOP's are read and understood. Similarly general procedures or non-technical procedures are implemented by "Read and Understood" documentation.
2. Training on SOP—generally a department head or QA head provides the training. It need not be any of the three people who are involved in completing a SOP. The person who provided the training should be competent enough to do so. For example if a SOP is issued by a corporate department, which is in a different location or country, it is not possible for corporate people to go to all the locations to provide training. In such case, concerned departments/ the QA head of the unit will take up training session to implement the SOP since they are considered as competent staff to provide the training of that particular SOP.

Whoever attends the training session, will have to sign in the attendance sheet irrespective of who wrote or reviewed or approved.

It is only to ensure the concerned people are trained to follow the SOP which is executed. There is nothing wrong to include the person who wrote and reviewed the SOP in the training session. If any of those who are competent enough to provide further training to second level, it can be done.

Respondent 3: Dear [Questioner], Training should only ever be carried out by people with a full understanding of the process AND who have been trained in Instructional Techniques.

A department manager/supervisor should be able to train his/her department on new versions of an SOP. I am assuming that the process has not changed, jut the SOP updated.

Please do not fall into the trap of reading and signing to indicate understanding. Most people are unwilling to admit in front of their colleagues that they do not understand something.

All training should be recorded with signatures/dates of both the trainer and

trainee. For complex tasks more than one training session may be required and the signatures should clearly indicate how far training has progressed.

Be careful of cascading training, it can be done, but you must ensure that the 15 people you trained, pass on the training with the same end result. Too often I have seen A trains B, B trains C, C trains D; what D knows and does is very different from what A knew and did.

For complex tasks I have written detailed training manuals so that everybody being trained receives the same information even when the training is by more than one trained trainer.

The most important part of training is a check to ensure that the knowledge and skill has been learned. The EU requires periodic checks on Practical Effectiveness. I use Skill and Knowledge questionnaires. Not only can these show that the training was effective, they can also be used for the periodic checks and point to the areas where re-training is required.

Having worked in the pharmaceutical industry since before GMP I have seen, and still see, the problems and errors caused by poor training.

Respondent 4: Hello, [Questioner], Here's my perspective on your SOP training questions:

A. Who can give the training? I would recommend that the author or co-authors of the procedure be trainers since they are the subject matter experts in the task. Your procedure on training should define SOP writers as "qualified" trainers.

B. Can the other SOP reviewers/checkers be considered as "trained?" To answer this, I would ask you, "How confident are you that they can perform the procedure without additional training or information?" Some firms write their procedures with a great amount of detail while others put less detail in the written procedure and supplement the procedure with extensive training. This is one of the places where you might want to do a simple risk assessment of your procedures and training approach. (I have seen some firms differentiate between those people who must perform a procedure and those, like managers, who simply need to know that the SOP exists and in general terms, what it includes.)

C. Training people who train others. In your scenario, I would say no. You should have "qualified" trainers who know how to present the information and have the content expertise. They should have an instructional guide (it can be simple) so you are confident that the consistent message is given during every training session. What would be better would be to provide a "train the trainers" course that is taught by the SME and that provides quite a bit of detail on procedure—for example:

1. What is the importance of this procedure?
2. What are the regulatory (GMP) reasons why we need to have this procedure?
3. What are the most important elements in this procedure (e.g., critical steps or substeps)?
4. How do you know when something is going wrong when using this procedure?
5. What are the most common mistakes or errors that can occur when using this procedure?

6. How do you document that the procedure has been completed?
7. What should you do when you sense that something isn't right?
8. What is the flow, steps and substeps of the procedure?

Also, those training on the procedure should use it themselves first so they have some practical experience.

D. Read and understand. Relying on this can be dangerous. Many firms use this approach and sometimes it will be adequate, but I (and many others in this forum) have had experience where people sign something and aren't paying attention to the details. (A recent experience showed that 25% of lab personnel signed that they had read and understood a procedure change but, 3 months later, had no idea that the change had occurred.)

One other question that I would ask is, "How do you know that after training people are performing the task properly?" This takes you into the area of assessment and evaluation.

The underlying issue on training and procedures is how confident are you that people will perform the task safely, effectively and in accordance with GMP principles. It goes beyond just compliance—there are business, technical and safety reasons why consistent task performance is so important.

Respondent 5: Hello [Questioner], Please find below the link to "A WHO guide to good manufacturing practice (GMP) requirements. Part 3: Training" (WHO/IVB/05.24). You may wish to look in Annex 5 (page 116), an example on how a vaccine manufacturer should conduct SOP training for lab staff, theoretical-read and understand-and practical training.

http://whqlibdoc.who.int/hq/2006/WHO_IVB_05.24_eng.pdf

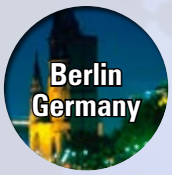
Respondent 6: Dear [Questioner]: Training should cover the content presented in the procedure along with the risk management techniques or operations. These risk management techniques include inputs from HSE departments also.

If you have a document reference section in your SOP, generally SOP training will cover all the aspects related to that SOP as well as knowledge on the referenced documents.

So training should be performed by the experts in that chosen activity who are aware of the risks related to that particular activity.

For example, a process validation protocol can be approved by QA, but in my view training on process validation should be performed by QA along with R&D, Production, QC and Safety department "incharges"/experts.

European Events Schedule



Workshop on Container/Closure Systems
Workshop/Exhibition: 29–30 April
Training Course: 28 April

Milan Training Course Series
Training Courses: 4–6 May

IG Meeting: Prefilled Syringes
Meeting/Exhibition: 27 May

2009 Biopharmaceutical Development and Manufacturing
Workshop/Exhibition: 16–17 June
Training Courses: 18–19 June

IG Meeting: Filtration
Meeting/Exhibition: 18 June

Workshop on Monoclonal Antibodies and Related Substances
Workshop/Exhibition: 25–26 June
Training Courses: 23–24 June

2009 Pharmaceutical Freeze Drying Technology
Conference/Exhibition: 29–30 September
Training Course: 1–2 October

IG Meeting: Rapid Microbiology Methods
Meeting/Exhibition: 21 Sept

QbD applied to Modern Aseptic Production and to APIs
Conference/Exhibition: 22–24 Sept

2009 Pharmaceutical Cold Chain Management
Conference/Exhibition: 6–7 October
Training Course: 8–9 October

2009 PDA/EMEA Joint Conference
Conference/Exhibition: 13–14 October
Training Courses: 15–16 October

Workshop: The Future of Glass as Parenteral Primary Packaging
Workshop: 26 October

The Universe of Pre-filled Syringes and Injection Devices
Conference/Exhibition: 27–28 October
Training Courses: 29–30 October

Sterilisation Technologies for Pharmaceuticals
Conference/Exhibition: 17–18 November
Training Courses: 19–20 November

PDA Parenteral Drug Association

2010 PDA Annual Meeting

March 15-19, 2010
Gaylord Palms Resort & Convention Center
Orlando, Florida

CALL FOR PAPERS

Dear Colleagues:

Manufacturers and distributors of sterile drug and related products face the challenge of optimal performance and improvement in an unprecedented economic environment. PDA recognizes that this challenge reflects a global need and that is why the Program Planning Committee for the *2010 PDA Annual Meeting* has chosen to emphasize this as the theme of next year's meeting.

The *2010 PDA Annual Meeting* will explore an area of immense importance to our industry – **Manufacturing Excellence**. The manufacturing of quality products is a keystone of our industry. Properly planned and performed process design, development, validation, sourcing, process control, contamination control, testing, handling, product and supply chain security, distribution and manufacturing all have an impact on **Manufacturing Excellence** and the cost of production.

We are seeking presentations on subjects related to **Manufacturing Excellence**. Almost all we do has a link to supporting the manufacturing process and creating an environment of quality and excellence. It is important to note and explore ways to improve yields and efficiency, to do more with fewer resources. Have you or a colleague in the pharmaceutical, biological, medical device or related industry who has been involved in or solved an issue related to **Manufacturing Excellence**? This is your opportunity to promote understanding and learning from collective experiences.

PDA encourages you to submit an abstract for presentation at the *2010 PDA Annual Meeting*, which will be held on March 15-19, 2010, in Orlando, Florida. Abstracts must be noncommercial, describe developments or work and significantly contribute to the body of knowledge relating to pharmaceutical manufacturing, quality management and technology. Industry case studies demonstrating advanced technologies, manufacturing efficiencies or solutions to regulatory compliance issues will receive the highest consideration. Abstracts related to sterile or related product manufacture are preferable, but those addressing other technologies are welcome. All abstracts will be reviewed by the Program Planning Committee for consideration.

Upon the creation of your user profile, you will receive an email confirmation from Oxford Abstract Management System containing submission instructions. Submissions received without full information will not be considered.

Please include the following information with your abstracts:

> Name
> Company
> Professional Title
> Full mailing address
> Email address
> Phone number
> 2-3 paragraph abstract, summarizing your topic and the appropriate forum (case study, discussion, traditional, panel, etc.)
> Take-home benefits
> Session objectives
> Rationale

Visit www.pda.org/annual2010 to submit your abstract today!

PDA is seeking presentations of 30 minutes in length, which present novel solutions and practical approaches. The following list is a guide of the suitable topics for papers. It is not exhaustive and any paper which fits the overall topic of the conference is welcome.

DEVELOPMENT SCIENCE

- Advances in Dosage Form Delivery Systems
- Automated Sterilization Technologies
- Contamination Control/Facility Manufacturing Control
- Cell Culture/Line Development
- Application of ICH Q8 and the Q8 Annex to process design and development
- Knowledge and Information Management
- Process Analytical Technologies (PAT)
- Process Modeling and Creation of a Design Space During Product Development

MANUFACTURING/PROCESS SCIENCE

- Aseptic Processing
- Automated Manufacturing Systems
- Barrier/Isolators/RABs
- Blow-Fill-Seal
- Building Management and Control
- CIP/SIP
- Multi-product Manufacturing
- Design/Management of Multi-Product Facilities
- Innovative Manufacturing Approaches
- Knowledge and Information Management
- Online In-process Testing (e.g. Container Closure/Filter Integrity, etc.)
- Production Strategies for a Global Market
- Robotics
- Visual Inspections
- Warehouse Control Systems
- Supply Chain Security

QUALITY SCIENCE

- Application of ICH, Q9, Risk Management to Quality Systems and GMP Compliance
- Compliance Monitoring and Trending
- Data Spreadsheet
- Qualification Case Studies
- Designing Pharmaceutical Quality Systems Across the Product Lifecycle, ICH Q10
- Environmental Monitoring
- Knowledge and Information Management
- Lean Manufacturing End to End (Supply Chain Manfacturing)
- LIMS and Lab Management Systems
- Microbiological Methods and Trends
- Quality Management Systems
- Supply Chain Management Security
- Supplier Quality Management
- Systems including Contract Manufacturing
- Tracking and Tracing Systems
- Training and Education Systems
- Validation of Pharmaceutical and Biopharmaceutical Processes

ABSTRACTS MUST BE RECEIVED BY JUNE 30, 2009, FOR CONSIDERATION.

For more information, please contact Wanda Neal, Vice President, Programs and Registration Services at (301) 656-5900, ext. 111 or Jason Brown, Programs Manager at ext 131

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When to identify ?

"Sequencing of the 16S ribosomal RNA gene to identify the class, order and genus of a microorganism is now an integral part of the approach to microbial taxonomy, but this gene is not useful for identifying many microbes at the species level."

Source: RECONCILING MICROBIAL SYSTEMATICS AND GENOMICS - ASM REPORT 2006

"With many isolates phenotypic identification is completely adequate and the added expense of using a genotypic identification system is not justified."

Source: PDA JOURNAL OF PHARMACEUTICAL SCIENCE AND TECHNOLOGY, 2008.

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When to investigate ?

"...it may be necessary to employ sensitive typing techniques to demonstrate that a microorganism isolated from the product test is identical to a microorganism isolated from the test materials and/or the testing environment."

Source: EP 5.1.9

diversilab Strain typing

Visit us at the 2009 PDA Annual Meeting in Las Vegas, April 20–21, 2009—Booth #513

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