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PDA Letter

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In This Issue:

PDA
Parenteral Drug Association

Connecting People, Science and Regulation®

U.S. Pharmacopeia Heavy Metals Workshop Aims for Regulatory Clarity

U.S. FDA Office of Generic Drugs Provides Answers to Residual Solvent Uncertainty

Emily Hough, PDA

Generic industry uncertainty over the U.S. FDA Office of Generic Drugs' (OGD) expectations for revised residual solvents compendial standards prompted the U.S. Pharmacopeia (USP), the industry and the Agency to preempt potential future confusion over a soon-to-be-revised General Chapter <231> *Heavy Metals*.

Taking a lesson from the regulatory implementation of USP General Chapter <467> *Residual Solvents,* USP held a two-day workshop called *Metals in Pharmaceuticals and Dietary Supplements* in April with the specific intent of helping the regulators and the industry agree on an implementation vector.

David Schoneker, Director of Global Regulatory Affairs, Colorcon, said that industry, FDA and the USP need to work together in order to effectively develop an "improved" control program for metals. Schoneker is the past Chairman of the International Pharmaceutical Excipients Council (IPEC) - Americas.

"There is a fair amount of controversy between different groups over the right approach to identifying the appropriate heavy metals to control and determining appropriate limits," said Schoneker. "I think we all recognize that if we don't get together and work closely with USP and FDA upfront in the development of this revision of <231> and fully understand what FDA will require in NDA and ANDA filings before it gets to the date of implementation, the implementation of a new approach to controlling heavy metals could be a much bigger disaster than what occurred last year during the implementation of <467> on residual solvents."

Workshop attendees representing industry, FDA and the USP met to review and discuss revisions to General Chapter <231> *Heavy Metals*, particularly metal impurities limits, methodology, risk assessment, harmonization and implementation strategies. USP anticipates that the chapter will be published sometime in 2010 and become official at a later date, allowing manufacturers sufficient time to incorporate changes in their processes.

Industry representatives aired a number of specific concerns and opinions about the revision and how it should be applied. Primarily, participants expressed their views on what should be included in the final revision and on how the regulatory authorities should interact with stakeholders to avoid uncertainty.

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DAY 1: inoculate test media, incubate **DAY 2:** agitate, examine, wait **DAY 3:** agitate, examine, wait **DAY 4:** agitate, examine, wait **DAY 5:** agitate, turbid? subculture **DAY 1:** inoculate test media, incubate **DAY 2:** agitate, examine, wait **DAY 3:** agitate, examine, wait **DAY 4:** agitate, examine, wait **DAY 5:** agitate, examine, wait **DAY 6:** agitate, examine, wait **DAY 7:** agitate, examine, wait **DAY 8:** agitate, examine, wait **DAY 9:** agitate, examine, wait **DAY 10:** agitate, examine, wait **DAY 11:** agitate, examine, wait **DAY 12:** agitate, examine, wait **DAY 13:** agitate, examine, wait **DAY 14:** read results

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The appropriate metals to control and at what limits are just two of the problems that industry, the U.S. FDA and USP are trying to solve before a revised general chapter on heavy metals can be implemented.

Coming Next Issue:
The Impact of the Microchip; Reports From the 2009 PDA Annual Meeting

Editor's Message

Don't Gripe...Work with Colleagues to Create Solutions!

We are using this issue to feature on the cover **Emily Hough's** latest report—a two-part report on how industry, the regulators and the pharmacopeias are working together to manage incredibly challenging implementation issues regarding USP's soon to be revised chapter on heavy metals and the recently revised chapter on residual solvents.

In the case of residual solvents, the realization that dialogue was necessary didn't occur until after the U.S. FDA Office of Generic Drugs (OGD) rolled out its expectations on the revised chapter. Nevertheless, an industry coalition worked with OGD and created mutually acceptable solutions. Taking a lesson from the residual solvents situation, many of the same players got together at a workshop earlier this year to attempt to forestall similar problems with the heavy metals revision. Wanting to assure a smooth transition to its revised chapter, USP stepped up and hosted the workshop.

PDA and its members work closely with regulators and other standards-setting bodies to deal with similar issues all the time. The recently published FDA draft guidance on validation is the perfect example. The document elicited a serious outpouring of opinions from our members. To help the industry and the Agency come to a better understanding of the new validation guidance, PDA has been hosting a series of workshops on the document. We've been doing the same with respect to supply chain, with our series of workshop on the topic concluding in June in China.

PDA's record of providing forums to discuss evolving regulatory issues is an important reason why professionals in the industry join and maintain membership in PDA. We held workshops in the past in direct response to new guidance or new developments, including quality systems, aseptic processing and GMPs for API's. The final testament to how effective PDA has been in bringing all sides to the table is the numerous joint conferences we've held over the last two decades, with the PDA/FDA Joint Regulatory Conference serving as the healthy and vibrant granddaddy to all of them.

So as you read this issue's feature articles, ask yourself what new guidances, regulations, or standards have been problematic for you. Then, get in touch with your colleagues and do something about it!

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PDA Customizes Advanced On-Site Training for Hospira, Inc.

The Parenteral Drug Association (PDA) is providing new, state-of-the-art training courses to Hospira, Inc., a world leader in specialty injectable pharmaceuticals in advanced aseptic processing, advanced pharmaceutical microbiology, current risk management concepts in sterile manufacturing and other topics.

The courses have been customized for different levels and types of personnel such as plant management, manufacturing supervisors and operators and quality control staff. Courses will be adapted from existing courses offered by PDA's Training and Research Institute (TRI) in Bethesda, Maryland.

"PDA is uniquely positioned to offer this advanced customized training," says PDA President **Robert Myers**. "We will do our best to make the training experience very positive. Our instructors are knowledge experts and have the capability to enrich the strong experience and skills of Hospira's plant staff and help advance its world-class manufacturing vision and commitment to operational excellence through an interactive training approach."

PDA worked with Hospira to modify the training based on discussions between the TRI staff and faculty and Hospira's management. All details of the training, including schedules, were established according to Hospira's specific needs.

"The training is hands on and user friendly," says PDA Senior Vice President for Regulatory Affairs & TRI **Robert Dana**. "The courses will be delivered in a practical, constructive, documented and cost-effective manner."

The Advanced Aseptic Processing course is designed for small groups of up to 15 students and will be taught by **David Matsuhiro**, Cleanroom Compliance Inc. David is currently the lead instructor for PDA TRI's flagship aseptic processing course taught at the Bethesda facility. Other courses will accommodate larger groups of students.

Three additional courses are on the agenda: "CAPA and Root Cause Analysis," co-taught by **Larry Mager** of Pathwise and **Tom Weaver** of Weaver Consulting, LLC; "Advanced Pharmaceutical Microbiology" to be taught by **David Porter,** PhD, Vectech Pharmaceutical Consultants, Inc., and "Current Risk Management Concepts in Aseptic Processing" by **Hal Baseman**, ValSource, LLC.

The training commenced in April and will be completed in the early summer, based on the availability of instructors and students.

2009 PDA/FDA Joint Regulatory Conference Keynote Speakers Look Ahead to 2020

Manufacturing, Healthcare Policy and Financial Outlook to be Discussed

PDA has confirmed three keynote speakers for the *2009 PDA/FDA Joint Regulatory Conference* who will discuss what the year 2020 will look like for the industry and what challenges must be overcome for the pharmaceutical industry, especially in the manufacturing segment of the industry.

Michael Bonney, President and CEO, Cubist Pharmaceuticals, **Jacqueline Scott**, Professor Harrison Institute for Public Law, Georgetown University, and **Barbara Ryan**, Analyst, Deutsche Bank, will get the meeting started with their expert opinions on where they expect the industry to be in 2020. Specifically, Scott will be presenting about views on public policy as it pertains to 2020; and, Ryan will be speaking about the financial analyst perspective on the pharmaceutical industry.

From September 14 -16, hear directly from FDA experts and representatives of global regulatory authorities, and take home best practices for compliance. Each year at this PDA signature conference, FDA speakers provide updates on 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.

To learn more about the conference, visit www.pda.org/pdafda2009.

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.

Science & Technology Snapshot

PDA Science and Technology Activities at an All Time High

Rich Levy, PhD, PDA

The number and quality of PDA science and technology activities are at an all time high. No matter how you measure it, the number of volunteers in taskforces, number of technical reports in-progress or published, or number of scientific meetings, PDA is on a roll. Thanks to the work of our Advisory Boards and the ideas of Interest Groups (IG) and members-at-large, this year's meetings line-up reflects both the interests of our membership as well as the challenges our members face in their daily jobs. Our active staff and members in Europe are contributing to this uptick too.

I took a moment to list of scientific meetings we have coming up that I have had some involvement in developing over the last six months. Some have never been held before, while others have already been held once or will be held in several different locations—something you asked for to ease the burden on travel budgets and time out of the office. An added benefit of offering a conference more than once is that it allows the planning committee to modify and improve the meeting agenda based on the feedback of the attendees at each previous event.

Here is a partial listing of science meetings coming up in the remainder of 2009:

- Process Validation Workshops in Chicago on June 8-9, October 26-27 in Bethesda and November 20 in Puerto Rico
- Biopharmaceutical Development and Manufacturing in Munich on June 16-17.
- Monoclonal Antibodies Workshop in Munich on June 25-26.
- Cell Substrates in Bethesda on July 29-30
- Rapid Microbiological Methods (RMM) in Frankfurt on September 21 – so new its not even on the web site yet!
- Global Microbiology in Bethesda on October 5-7
- Sterilization Sciences in Puerto Rico on November 18-19

As an organization, we have made a strong effort to provide services to the biopharmaceutical side of the industry in recent years. In 2009, we already held a meeting on Mycoplasma in Berlin in March, and we are holding events on Monoclonal Antibodies in June and Cell Substrates in July. The former is a by product of our 60+ membership Mycoplasma Task Force led by **Barbara Potts** of Genentech, while the latter is the result of discussions in our BioTech IG and Advisory Board, as well, as the capable leadership of **Mike Wiebe,** PhD, (Quantum Consulting, LLC) and **Kathryn King,** PhD, (CDER, FDA) who have along with their planning committee created a completely new agenda based on industry needs. This meeting will be held immediately after the CaSSS CMC Strategy Forum meeting being held in Bethesda, Md. too.

And what about two of our members favorite areas, sterilization and microbiological sciences? We are holding a new series of sterilization conferences (I am traveling to one in New Jersey as I write this column), which includes a great presentation by Baxter Healthcare on new sterilization methods they are exploring, as well as a very interesting paper on chlorine dioxide sterilization, a topic once reserved for drinking water treatment and the sterilization of animal facilities. And my own favorite, the 4th Annual Global Microbiology meeting which will feature two keynote speakers, **Stephen Denyer**, PhD, Cardiff University, addressing moving lab micro technologies to the manufacturing floor, and **Paul Sturman**, PhD, Center for Biofilm Engineering, addressing biofilms and their control in pharmaceutical water systems. The latest Rapid Microbiological Methods meeting to be held this fall in Frankfurt will feature the participation of three European regulators as part of our one-day discussion on the implementation of rapid microbiological methods. A global meeting planning committee is ensuring that this meeting in Frankfurt takes a global perspective on challenges we face applying new to existing manufacturing processes.

Last but not least, our workshop on the new U.S. FDA draft guidance on Process Validation. We quickly organized a series of meetings on the draft, which has included the participation of **Grace McNally** and **Brian Hasselbach** of CDER. These meetings also include discussions on legacy systems, the application of statistics to process validation studies, and offer a chance to ask the FDA speaker questions and to contribute to PDA's efforts to facilitate the implementation of the draft guidance.

All in all, it's going to be a great year, and I hope you can join us as we keep the momentum giving in science and technology at PDA. Don't hesitate to offer your ideas, too–that is how all this activity was started in the first place.

[**Editor's Note:** See related articles on the March Mycoplasma meeting, p. 42 and the upcoming Cell Substrate and Microbiology meetings, p. 36 and p. 39, respectively.]

Call For Scientific *Posters*

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

The PDA Cell Substrate Workshop Program Planning Committee invites you to submit a scientific abstract for poster presentation at the *2009 PDA Cell Substrate Workshop*. Abstracts for posters are being sought on all aspects of viral testing of cell banks and unprocessed bulk, new cell lines, and raw materials associated with cell substrates

All abstracts will be reviewed by the Program Planning Committee for inclusion in the meeting poster presentations.

Submit your abstract to **Andrea Viera** at Viera@pda.org; abstracts must be received by June 30 for consideration.

PDA Journal *FAQs*

How can I access the latest issues of the PDA Journal?

While PDA works with Stanford University's HighWire Press to create a new and permanent home for the PDA Journal, PDA members can access their *PDA Journal* online at www.pda.org/journal. You must login using your PDA Member ID and password to download the issue.

How will I know when a new issue is published?

PDA will contact you via email when a new issue of the PDA Journal is ready for viewing. We encourage you to update or reregister your email to ensure you receive these notifications. Go to www.pda.org/update. Already opted out of PDA emails? Opt back in at www.pda.org/email.

Who do I contact if I have troubles logging in?

The PDA Membership Department is always here to help! Contact us at: info@pda.org or (301) 656-5900 ext. 100.

What new features will we have when the Journal moves to HighWire?

See the February and April 2009 Science and Technology Snapshots for details on the upcoming Journal website hosted by HighWire Press.

Recent Sci-Tech Discussions: Residual Solvents; Organic Solvent Residue in Cleaning Validation

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.

Residual Solvents

Questioner: Dear Members,

Can anyone shed some light on "testing drug products for residual solvents?" We have a sterile injection solution product which we don't use any solvents (except WFI and HCl) during the manufacturing process, so I would assume it is not required to do gas chromatography (GC) testing of the drug product for solvents. However, someone told me that the U.S. FDA will, though not required, recommend testing it anyway. I am confused because once the testing is performed, no one can really guarantee that the chromatogram is as clean as it should be. Please comment.

Respondent 1: [Questioner], If you certify that no solvents are used and you further certify that no solvents are generated by your manufacturing process you may be able to justify not testing by GC.

Respondent 2: Have you considered the ICH guideline on the topic for assistance?

Regards.

Respondent 3: [Questioner], Aside from your vehicle and excipients, bear in mind your main active may indeed contain residual solvents. Regularly, a cumulative procedure may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product. If the calculation results in a level equal to or below that is provided in the guidelines, no testing of the drug product for residual solvents need be considered. If, however, the calculated level is above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount.

Having said that, even if you are on the safe side, you may still find some regulatory reviewers enquiring about adding residual solvents as part of your drug product release specifications. Nonetheless, there's no need to physically perform the test. Simply state in the results section: "Complies with Option 1 (or 2) as per USP<467>." Hope this helps!

Respondent 4: [Questioner], What about the residual solvent content of the API and any other excipient(s) used in the injectable product. According to your vendors, are they made using any Class I or Class II solvents? If so, have you calculated your PDE taking all components into consideration?

Respondent 2: [Respondent 4], Spot on! One special issue to look out for: toluene is sometimes used in the manufacture of excipients or APIs. The toluene often contains trace quantities of benzene, so controls for residues of benzene (= Class I) may be required.

Regards.

Questioner: Thanks, [Respondent 2].

Actually, it is the USP that requires this residual solvent testing. I am just not sure about FDA's stance on testing of all drug products regardless of processing a drug product with and without use of solvents. I know I may do away without testing it.

By the way, since this is an injection product, do you know if I must submit a microbiology copy in my ANDA with a white folder besides the red colored folder for the chemistry copy?

Respondent 5: In August 2008, the FDA published a guidance for industry which is entitled, *Residual Solvents in Drug Products Marketed in the United States*. This is the FDA response to the USP's new requirements. I think that reading this guidance will answer most of the questions. Best regards.

Respondent 2: [Questioner], It is also in the Ph. Eur. But the original text is the ICH guideline of which the others are closely based. The difference is that the ICH text is a guideline and the pharmacopoeial texts are presented as applying in a mandatory context. The Ph. Eur text could be seen as applying to all substances for pharmacopoeial use, not only those with a pharmacopoeial monograph. The European pharmaceutical legislation makes it compulsory to follow relevant pharmacopoeial texts. Regards.

Respondent 6: Residual benzene can contribute from toluene, acetone and hexane used for API manufacturing. Frequently regulatory agencies recommend monitoring of benzene in APIs, if these solvents were used in the process, although not used in the process directly. But in any pharmacopia for these three solvents there is no mention of a benzene limit. Please share any such type of limit for benzene in toluene, acetone and hexane used in industry.

Hexane is a mixture of n-hexane, methylcyclopentane, cyclohexane, etc., different hexane fractions. The limit of hexane as n-hexane (Class II) is 290 ppm and for cyclohexane (Class II) as 3880 ppm as per Q3C. In the residual solvent chromatograms also have different fractions that are noticed in APIs. In the API industry where hexane is used in-process, how is it determined and what will be the limit? Regards.

Questioner: Thanks, [Respondent 2]:

This case is now getting more and more interesting and I think this may be a good chance for all of us to learn the lesson. I did follow the Ph. Eur guideline and tried to escape from testing the drug product for the residual solvents as we did not use any to manufacture our injection product. However, when I saw this USP requirement and FDA's guidance in August 2008, I thought it would be smart for us to test my product. So, I ordered our QC to do it anyway. Then it became my nightmare since because we have found a very small EtOH peak in the GC for every sample we have tested. We went through hell to start the OOS and investigation at various levels of operation and still could not understand how this EtOH has gotten in my product in the first place. It is now in my audit trail and I can not close the CAPA. It is absolutely impossible for the disinfecting alcohol to get into my aseptically filled vials. So, have any better idea?

Respondent 7: I agree with [Questioner]. This is why it is always recommended that some batches of product (be it drug substance or drug product) should be analyzed with appropriate method and do scientific evaluation together with solvents used in ingredients, process and byproducts if any. And then appropriate recommendation should be made whether it is appropriate to analyze or not.

There are numerous guides available suggesting reduced testing, but each guide demands theoretical (scientific evaluation) and practical (analytical data) support to the rationale.

Respondent 5 : Hi [Questioner],

First have you carried out blanks to make sure that it is not an artifact of the method? Also check all your non-ethanol solvents for the presence of ethanol. There are some solvents which have a small amount of ethanol present as stabilizers.

The fact that it is present in every sample should actually make it easier to find the root cause. If it was in some and not in others it would be a lot more difficult.

Respondent 8: Dear colleagues, Regarding this topic, if all residual solvents are tested in raw material and the results are acceptable, is it still required to perform residual solvents tests in final product? Thank you in advance.

Respondent 5: The answer will of course depend on which jurisdiction you are in. To my mind it seems that the USP and FDA are setting the pace on this one, and if you intend to follow their line, the answer to your question is in the following quote from the recently published guidance for industry: *Residual Solvents in Drug Products Marketed in the United States* from the FDA, *Current General Chapter <467> allows direct testing of finished drug products for residual solvents to* ➤

determine compliance. However, new General Chapter <467> provides options for testing the active pharmaceutical ingredient and excipient components of the finished drug product for residual solvents; it also provides for using these test results to determine whether the finished drug product complies with the test limits. If the test limits are met, finished product testing is unnecessary. Regards.

Respondent 9: "If all residual solvents are tested in raw material and the results are acceptable, is it still required to perform residual solvents tests in final product?"

A) If solvents *are* used in the manufacturing of the final product, then yes, the final product must be tested.

B) If solvents *are not* used in the manufacturing of the final product, then it depends.

You can use a calculation based on the results obtained from the raw material testing to see if the final product needs to be tested. The calculation needs to take into account each solvent from each raw material used and the percent composition of the raw material in the final product. If the calculation shows you are below the limits, you do not need to test. If your calculation shows one of the solvents is above the limit, you need to test to see if the manufacturing process removed enough of the solvent so that it meets the limit in the final product.

To make things easier in (B), if each residual solvent in the raw materials met the limit in the guideline (ICH, USP, etc) then the calculation does not need to be performed as the final product will meet the limits (again as long as no solvents were used in the manufacturing of the final product).

Questioner: I agree with [Respondent 8]. Our case used only HCl to adjust pH and sodium chloride for tonicity. The API was tested without traces of EtOH. So, why should there be testing of residual solvents in the drug product? Testing residual solvent had given me a nightmare after EtOH showed up in my GC, and I just cannot make this a case telling the FDA that because my disinfecting solvent has flied into my vials and in every one of the 10,000 vials. There is not much, but it is detectable in GC of this EtOH.

Any more suggestion as to where this solvent may have come from?

Respondent 7: There is a EMEA guideline for this. If you control Class II solvents with a limit of 10% less than the ICH limit in appropriate intermediate/ starting material, then routine control at final product stage is not required (e.g., acetonitrile ICH limit is nmt 410ppm and then it should be controlled less than 41ppm). Similarly, Class 1 solvents should be controlled less than 30% of ICH limit.

We can extrapolate this justification to Class III solvents also and most of the time it is accepted by authorities.

You have to control solvents used in the final stage of manufacturing in final product (there is no intermediate then!!!!).

Respondent 4: This depends on your process for formulation of your drug product. If it is possible that reactions could occur between excipients, API, solvents and container closure systems during the production and packaging processes and one or more residual solvents could be a result, the drug product should be tested for the possible reaction product. If the process requires heat, moisture, high mixing speed or one or more other rigorous step which could induce reactivity between components, then a drug product should be tested for viable solvents and compared with the summation of each solvent from all components determined individually. The differences, if any, will indicate whether one or more solvents are formed due to the formulation process.

[Editor's Note: For more information on the implementation of USP's revised General Chapter <467>, see cover story and article on p. 18.]

Organic Solvent Residue in Cleaning Validation

Questioner: Hi! Need your inputs regarding the mentioned subject.

As per cleaning validation approach followed in industry, residue of previous product API is detected and quantified as a measure of risk of cross contamination and limits are also calculated based on API.

Now if one of the formulation organic solvent based granulation or liquid (like alcohol, dichloromethane, etc., as applicable), is it required to estimate the residual solvent in cleaning validation? Solvent is one of the excipient. What is the requirement?

Respondent 1: I would think that testing for residual solvents as cleaning residues would depend on the miscibility/solubility of the solvent(s) and the rigorousness of the cleaning process. However, in my experience with development and validation of cleaning processes, the solvents are quite volatile and soluble, especially with a detergent present and will not need to be analyzed as a residual. If a fairly innocuous alcohol, this would be true. However, if a Class II (USP residual solvents procedure) or more toxic solvent is for some reason used in the formulation process, proof from a single batch evaluation may be needed.

Questioner: Dear [Respondent 1],

Thanks for your reply. I request further clarification from you.

I came across a case, where a tablet formulation is manufactured using dichloromethane (MC) + isopropyl alcohol (IPA) combination during process (organic solvent based granulation). As such, MC is sparingly soluble in water but soluble in alcohol. So I consider that in combination IPA, it will also be soluble in water. Hence will easily go away.

First criteria for visual inspection after cleaning is equipment that should be dry and on inspection surfaces which are dry MC (Class II) & IPA (Class III)

is easily volatilized. Is it possible that dried surfaces may have traces of organic solvents? I think *no*.

In such scenarios, are there any requirements to analyze residual solvents? Can the above justification convince inspectors? Thanks in advance.

Respondent 1: [Questioner], It in part depends on the proportion of methylene chloride used in relation to IPA. If MC is significant, it may not be that miscible with the cleaning solvent. The fact that the surface appears to be visually clean needs to be interpreted quantitatively and perhaps could indicate that MC is still present at low levels but at levels that are detectable. As I mentioned in my response, being that MC is a Class II compound and a solvent of concern, I would at least subject the equipment surface from processing of a single batch to either swab or rinse sampling (rinse could be IPA) immediately following cleaning/drying. The sample should be quickly analyzed by GC for any traces of MC. You are correct in stating most if not all of the MC and IPA will evaporate from the surface upon drying. However, considering the concern over trace MC levels, the single testing will provide some back-up support if the subject elicits regulatory concern, especially if the equipment will be used for a completely different type of granulation subsequently.

[Respondent 2]: Dear Colleagues, Has anyone had the experience of validating the dye immersion method for container/closure integrity test of a sterile injection product? We have this C/C tested by West Pharma using their helium leak test method (a very sensitive method as far as I know) on empty sealed vials and the probability of contamination was <0.01 which is very good. But, as for using it in the stability study, we have to use a validated dye immersion method on vials containing our drug product solution. Can someone shed some light on the validation method with a good "sensitivity" of the C/C system?

Respondent 3: [Respondent 2], The New England PDA Chapter is actually having a meeting on this subject in the Boston, Mass. area this coming Wednesday (March 11, 2009). **[Editor's Note:** The meeting has since passed, but be sure to check out New England's website for upcoming meetings of interest.]

Logon to join the discussion.

Go to:

www.pharmweb.net/pwmirror/pwq/pharmwebq2.html

PDA Interest Groups & Leaders

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

SECTION TITLE

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

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PDA Parenteral Drug Association

2010 PDA Annual Meeting

March 15-19, 2010
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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:

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> 2-3 paragraph abstract, summarizing your topic and the appropriate forum (case study, discussion, traditional, panel, etc.)
> Take-home benefits
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> Rationale

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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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U.S. Pharmacopeia Heavy Metals Workshop aims for Regulatory Clarity, continued from cover

The following list outlines other important conclusions reached during the workshop regarding revised <231>:

- New <231> should:
  1. focus on the top four metal impurities: inorganic arsenic, cadmium, lead, and methyl mercury
  2. propose methodology but allow flexibility to apply any validated test method
  3. focus on metals that are part of the normal compositional profile of a substance from typical sources and provide clarity that other random metal impurity contamination must be handled as foreign substances and impurities (per USP General Notices, Tests and Assays)
- A new general chapter should be considered for expected metal impurities from catalysts and reagents that are aligned with the EMEA guideline (EMEA/CHMP/SWP/4446/2000)
- Implementation process requires significant involvement of FDA to determine their position regarding an acceptance of planned strategy, a definition of "likely to be present" and a definition of expectations associated with regulatory filings

To ensure that the heavy metals chapter is implemented correctly, Schoneker said that discussions need to take place between industry and regulators as they did in the case of the residual solvents chapter, however these discussions must take place before implementation, not after implementation as was the case with Residual Solvents.

Not long after the FDA generic office's expectations for USP <467> began to manifest, a number of leading trade organizations and PhRMA came together to form the Coalition for Rational Implementation of USP General Chapter <467>. (See box on page 19.) Schoneker serves as coordinator for the group, and said that a similar coalition has been formed to deal with USP <231>.

To ensure that the heavy metals chapter is implemented correctly, Schoneker said that discussions need to take place between industry and regulators as they did in the case of the residual solvents chapter, however these discussions must take place before implementation, not after implementation as was the case with Residual Solvents.

The <467> Coalition worked directly with FDA to gain further clarification of what FDA was expecting from firms during ANDA submissions and GMP inspections. In October, FDA participated in a face-to-face meeting with Coalition representatives to answer a number of questions and then posted to their website a Q&A document based on the dialogue.

In November, the Coalition came back to FDA with additional questions, which led to a teleconference during which FDA answered the questions to provide

Generics Industry Comes Together

The controversy over what FDA initially expected in ANDA submissions led to the initial meeting of the Coalition, David Schoneker said, and it is made up of members from the International Pharmaceutical Excipients Council of Americas, The Generic Pharmaceutical Association, the Consumer Healthcare Products Association, the Pharmaceutical Research and Manufacturers of America and the Society of Chemical Manufacturers and Alliance's Bulk Pharmaceutical Task Force. The Coalition was formed and met with FDA last year and came up with questions about Testing vs. Control, Identification of Class 3 Solvents, Use of Class 1 Solvents, and the Need of Immediate Relief While Awaiting a Revised Guidance. The meeting on Oct. 10, 2008 lead to a "clarification" of the guidance on Oct. 28, 2008 in the form of the initial Q&A document.

He said the type of coalition that was put together is almost unprecedented in the past. "Typically you have the generic companies coming down one way, innovator companies coming down another way, the supplier industry coming down a little differently or maybe two of those aligning with each other. But rarely do you ever get everybody who pretty much represents the whole industry on one side of the issue. I think what we found was that when you can work together as a coalition on issues where there is a common message and there is a common interest it is an extremely beneficial thing to do to work together, and I think it sends a clear message to FDA that something is wrong when the entire industry stands together like this. I think we got FDA's attention when we all got together and they told us they were a bit surprised that we formed this coalition.

"I think what we learned in this effort was that a coalition like this, should be able to exist whenever we need it. I think the real key here is the concept of this coalition will go on for issues where it makes sense. I think we will reenergize this coalition whenever needed, where we have a kind of issue that needs this kind of coalition support. Next up….Heavy Metals!"

additional clarification on FDA's expectations. The Coalition recorded each of the answers to their questions, and designed their own Q&A document to serve as industry guidance regarding the additional questions. This new document was reviewed with FDA to verify that all the answers represented the Agency's current thinking discussed during the teleconference. This new document was shared with FDA and then posted to the IPEC Americas website.

The Coalition believes that this document will help companies better understand FDA's expectations when filing residual solvent information with ANDAs and NDAs. Schoneker indicated that the Coalition has sent the industry Q&A document "around to all the Coalition member organizations with the idea that they should provide it to all of their members to assist them in understanding FDA's expectations. We will then discuss the information obtained during these meetings with FDA in public forums to try to get that information out to companies that are not members of the Coalition."

> ***"There seems to be a real willingness on the part of FDA to continue the discussion with industry as long as we need to continue it and are asking good questions to make sure that everybody is clear."***

As Schoneker said, "The good thing about the coalition that we built for the residual solvents was that it got us into a position of having an ongoing dialogue with FDA. I think everybody realized the benefit that that had. I think we see that as a desire of all parties on things like heavy metals as well. Lets get that dialogue started, lets keep it going and start it early. So, if we have these kind of discussions on heavy metals, prior to implementation, with USP and FDA, I think you will see this coalition help resolve issues before regulatory filings end up getting delayed or rejected due to confusion on what is expected. Members of other trade associations may also want to join the coalition as we move forward with heavy metals if they have a significant interest in the outcome of these discussions."

He continued, "There seems to be a real willingness on the part of FDA to continue the discussion with industry as long as we need to continue it and are asking good questions to make sure that everybody is clear."

[**Editor's Note:** The Q&A can be accessed at http://www.ipecamericas.org/public/whatsnew.html]

Stricter Solvents Requirements by FDA's Generic Office Pose Problems for Generic Companies

Emily Hough, PDA

U.S. FDA's generic drugs (OGD) and new drugs offices have taken different approaches with applicants in implementing the revised USP General Chapter <467> on Residual Solvents. OGD's interpretation of the Chapter is viewed by generic companies as burdensome, since it requires more information in ANDA submissions than previously required in NDA submissions to demonstrate that Residual Solvents are in compliance with appropriate standards.

Factoring into the discrepancy in application of the new chapter is the fact that the new drugs side started requiring the tenets of revised <467> in 1997 with the adoption of International Conference on Harmonisation (ICH) guideline on residual solvents (Q3C). OGD, on the other hand, has had less than a year to refine its practices since they are responding directly to the revised USP chapter.

USP General Chapter <467> on Residual Solvents was targeted for revision following the publication Q3C. USP initially held off revising <467> to match Q3C, but began working on the rewrite in the early 2000's.

Final publishing of the new chapter was delayed two times before it was finally released in 2008. At first, the effective date for the revised <467> was January 2007, but the standards-setting body elected to delay implementation until July 2007 because of industry concerns. During this period, a joint PDA/USP training workshop on residual solvents revealed deeper industry problems with the chapter. In response, USP officials at the workshop suggested during the meeting that an additional delay in implementation was "on the table" though unlikely. The PDA Letter reported that "only a strong demonstration of support from industry would spur USP to enact an additional delay to implementation." [**Editor's Note**: Read more about the workshop in the March 2007 *PDA Letter*, p. 12.] Prompted by such "strong demonstrations" following the workshop, USP indeed suspended the chapter effective date until July 1, 2008.

Neil Schwarzwalder, Quality Consultant, Compendial Affairs, Eli Lilly, said that the PDA/USP workshop helped USP in part to identify areas in which to modify the chapter. "[USP] made some changes as a result of the meeting and there were some modifications to the chapter as well." Schwarzwalder attended the 2007 meeting as a representative of PhRMA. He also credits companies who were unaware of the impending USP implementation for having a helping hand in delaying the chapter.

At the 2007 meeting the main concern was about validating current methods against the methods specified in <467>. Schwarzwalder said that the one-year delay wasn't as important for large innovator companies. He cited Eli Lilly's ➤

<467> Coalition–FDA FACE-TO-FACE MEETING PARTICIPANTS

Last autumn, representatives of the FDA participated in a meeting with the Coalition for Rational Implementation of USP General Chapter <467> to answer questions. The following is list of FDA and industry participants in the meeting.

FDA Center for Drugs Evaluation and Research Representatives

Helen Winkle, Office of Pharmaceutical Science
Lawrence Yu, Office of Generic Drugs
Gary Buehler, Office of Generic Drugs
Keith Webber, Office of Pharmaceutical Science
Jon Clark, Office of Pharmaceutical Science
Frank Holcombe, Office of Generic Drugs
Larry Ouderkirk, Division of Manufacturing Product Quality
Cheryl Kaiser, Office of Pharmaceutical Science

Coalition representatives (affiliation indicates organization represented, not company)

David Schoneker, IPEC Americas
Priscilla Zawislak, IPEC Americas
Gordon Johnston, GPhA
Melissa Figgins, GPhA
Steve Sutherland, GPhA
Rachael Roehrig, CHPA
Sue Beavis, CHPA
Saul Gylys, CHPA
Barb Ferguson, PhRMA
Brant Zell, SOCMA BPTF
Lynn Jones, SOCMA BPTF

experience as an example: "[Eli Lilly] had been applying ICH guidelines since 1997/1998. We have already had a lot of experience with it."

He said that updating older products to the "current" USP standards required extra effort for Eli Lilly. "The basic challenge for us was to extend ICH to all these other items that it hadn't been formally applied to before and get rid of the Organic Volatile Impurities requirements which were really in conflict with ICH and didn't match up well."

While he believes that the extension was not "that significant" for the innovator companies, Schwarzwalder thinks "it helped some of the smaller ones."

Indeed, the generics industry has struggled with implementation of <467>, particularly with respect to the FDA Office of Generic Drugs expectations.

Schoneker, said industry felt they understood what FDA would be expecting with respect to the chapter, since this was "not new" and "ICH Q3C (and effectively <467>) has been out there for ten years." In practice that turned out not to be the case.

Culpability for the disconnect, **David Schoneker,** Director of Global Regulatory Affairs, Colorcon, said lies with both industry and FDA. "[Industry] didn't push the point far enough to get the right answers and implemented <467> in the manner that it thought FDA wanted it to be implemented based on experiences with NDA submissions." The problem, according to him, was that once <467> became official on the generic side, industry felt blindsided with the types of testing and other information that the reviewers in OGD wanted to see in an ANDA application. Industry viewed OGD's initial expectations as going "way beyond what <467> even calls for," he said.

Schoneker pointed to OGD's initial expectations for class 3 solvents as an example. He explained that <467> "clearly states in black and white that for residual solvents which are identified as class 3, if they are there at less than 0.5 percent, there is no need to even identify what solvents they are. OGD's initial expectations were 'No, you have to identify and test for every one of them and put all that information into your ANDA.' Nobody in their wildest dreams would have thought that that was what FDA would expect, because <467> clearly states that you don't have to do that." This issue was later resolved in the discussions with FDA.

Another area at issue, according to Schoneker, is how to ensure the integrity of supplier data. He explained that since nobody wants to do redundant testing, industry was following the language in <467> which stipulated that only limited testing of drug product components was necessary when a qualified statement was provided from a supplier that certifies that an API or excipient or other material does not contain specific solvents, or in fact contains solvents at acceptable levels. Based on these certifications, users believed that they were not required to conduct testing and could use the suppliers data in calculations to show that the drug product is lower than the requirement.

Schoneker said that the companies making new drugs have been using these kinds of qualified supplier statements to show that they comply and justify their submissions for years and nobody had asked any questions in the past, so everybody assumed this would also be acceptable for OGD. Testing of all components has not typically been done by many companies if appropriate qualified information was available from the suppliers to support the Q3C compliance claims for the drug product. USP <467> also provided for the routine use of qualified supplier statements to demonstrate compliance.

OGD, however, promulgated a stricter standard of implementing supplier compliance than what had previously been done with new drugs, essentially requiring that companies not rely solely on vendors' statements. If "you have not completely qualified your supplier," Schoneker said, "you can't just blindly trust a statement you got from your supplier." Complete qualification would include audits, utilizing third party auditing bodies where appropriate, to verify the supplier meets GMP requirements and the statements that the suppliers are making about residual solvents are shown to be adequate and accurate, he explained.

Schoneker stated that IPEC Americas supported the requirement that all of these supplier statements needed to be qualified (or verified) by the drug product manufacturer before they could be accepted. However, industry felt that this type of information was primarily a GMP issue not something that needed to be included in regulatory submissions. OGD felt otherwise, and wanted to have

qualification information included with the ANDA filings. He said that some generic drug companies may not have fully understood how much supplier qualification is necessary and this did create some implementation problems with OGD since they were looking for this information in the ANDA."

FDA spokeswoman **Karen Mahoney** said that the reason for the differences in the way the FDA's Office of New Drugs and OGD have implemented this policy of compliance is because of the different approaches both offices take with applicants. On the new drug side the FDA can inform their policy on residual solvents when they meet with the sponsors, which is not possible for OGD due to the large number of applications. Mahoney reiterated that manufacturers of new drug products have been expected to comply with ICH Q3C since Q3C was issued in 1997 and limits on residual solvents in USP <467> are those that are found in Q3C. But OGD only had the unofficial FDA Q&A document to facilitate the implementation of USP <467> for generic drugs.

Speaking through Mahoney, **Helen Winkle**, Director, OPS, and **Lawrence Yu**, PhD, Director for Science, OGD, informed the *PDA Letter* that there was extensive discussion of the revision during this period within OGD. This was considered a high priority issue because it was affecting a significant number of ANDAs.

As its interim solution to the supplier qualification problem, FDA is allowing any pending ANDA's to be moved forward as long as FDA has a commitment from the company that they are going to show that that supplier is qualified. Companies have six months to build the case by way of auditing, evaluations and confirmatory. Come July 1, 2009, FDA is going to expect that everything that it is looking for will be put in a submitted ANDA, and after July 1 there will be no more six month provision; either companies are going to supply ANDAs with the qualification information that FDA is expecting to see or the ANDA will be rejected. Mahoney said that OGD would like to stress that "ANDA sponsors are responsible for their choice of excipient suppliers and should work with those suppliers to ensure the quality of excipients used in drug products."

According to Schoneker, FDA is willing to accept qualified statements, but it is going to expect companies to have a really solid backup to show that the supplier has been qualified in lieu of doing that testing.

Schoneker said that the Coalition is "definitely happy with the changes that were made. I think [the FDA] did a lot to address a lot of the key questions that we had and where things were unclear. We are very happy about the outcome of the meeting that we had with FDA which resulted in the Q&A document that came out. This interaction opened a very open dialogue between the coalition and the FDA about these issues."

Quality & Regulatory Snapshot

Health Authority *Special Report*
Agency Focuses On Strategies To Better Predict, Prevent Economically Motivated Adulteration

Emily Hough, PDA

The U.S. FDA is developing strategies and standards to better prevent adulteration and counterfeiting within the drug, medical device, cosmetic and food industries.

One of those strategies was to hold a public meeting called *Economically Motivated Adulteration Public Meeting* on May 1 with members from the drug, medical device, cosmetic and food industries to discuss their insights into how to best prevent or predict economically motivated adulteration (EMA).

According to **Randall Lutter**, Deputy Commissioner for Policy, Department of Health and Human Services, FDA, the reason why cases of adulteration and counterfeiting has resurged in recent years in such products like heparin, powdered milk and pet food, is due to globalization. "A large part of the United States consumption is now imported, and this is something that is relatively new in the last decade or so. That creates all sort of new challenges. Protection at the border is intrinsically more challenging. Inspections are more costly overseas, equivalent state regulatory agencies do not exist and other information is scarce." Lutter said that the volume of imported FDA regulated products has grown about 14% annually since 1997.

At the meeting, a working definition of EMA to bring a common understanding to participants was given. EMA was defined as "the fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain. EMA includes dilution of products with increased quantities of an already-present substance (e.g., increasing inactive ingredients of a drug with a resulting reduction in strength of the finished product, or watering down of juice) to the extent that such dilution poses a known or possible health risk to consumers, as well as the addition or substitution of substances in order to mask dilution."

Lutter stressed, that all manufacturers and sellers of FDA regulated products have a part to play in solving EMA, and that it was not just an Agency issue.

Martin Van Trieste, VP, Quality, Amgen, who serves as the chairman of the Pharmaceutical Research and Manufacturers of America's (PhRMA) Quality Technical Group, said that the recent highly publicized events highlight the fact that unethical players and criminals have entered into the supply chain in unprecedented levels, and that everyone must be prepared for the next surge of adulterated products.

Echoing warnings he has been making at the PDA/FDA Pharmaceutical Ingredient Supply Chain Conferences (which con-tinue in June in China), Van Trieste stated: "We must all realize, if this is going to happen again, it is when and where it is going to happen again. These issues are of extreme importance to pharma and pharma member companies, and we must realize that pharma is a heavily regulated industry. We have new drug applications and approval processes for our products, we follow good manufacturing practices, but those regulations keep honesty on us and we have to realize that the criminal element has now entered into the system."

The "Swine Flu" is the perfect example of an opportunity for unethical players to engage in economically motivated adulteration of products, according to Van Trieste. "The world is in short supply of antiviral agents, and governments all around the world are trying to increase their stockpile so they can inoculate their population. It's the perfect opportunity in the triangle for someone to come in and to make a quick buck. So now knowing that, we must stop, think like criminals so we can predict what a criminal would do. How would they/what would they use for an economic adulteration? How would they go about it? Maybe once we know that, we would have a better chance for detecting the adulteration."

Van Trieste said that with additional resources, the Agency can enhance inspection efforts abroad and ensure a safe and secure supply chain. "We also believe that the FDA should increase the number of GMP inspections it conducts overseas, particularly of active pharmaceutical ingredient manufacturers," he said. "These inspections should also focus on good distribution practices and the authenticity of data submitted to the FDA. The FDA should also require all entities supplying material as used for finished products, to be registered with the Agency if the finished products are sold within the United States, and should require regular updates to

these registrations." He said that this would help promote transparency in the pharmaceutical supply chain.

Industry might not need to wait long for an enhanced FDA. The U.S. Congress is working on two bills to beef up the Agency; one in the Senate and one in the House of Representatives, both with the purpose of amending the Federal Food, Drug, and Cosmetic Act. The bills already have been referred to their respective committees.

The U.S. Senate bill is called *The Drug and Device Accountability Act of 2009,* and was introduced by Senators Charles Grassley (R-IA) and Edward Kennedy (D-MA). The bill includes a number of provisions to enhance the Agency's ability to respond to unsafe drugs, including:

The destruction, not reworking, of drugs which are considered defective and may cause injury or death

Enhancement of FDA's IT system, which would include listing registered facilities or "establishments" and compliance histories on a database

Civil penalties possible for any manufacturer, distributor, importer, broker, or filer that violates a requirement of the Act

A dedicated foreign inspectorate

Regarding the latter, the Act calls for a "corps of inspectors" who are dedicated to inspections of foreign "establishments" to be organized into four units. The units will be made up of inspectors that have expertise in the inspections of food facilities, human drug facilities, animal drug facilities and medical device facilities.

The House of Representative bill, entitled, The *Food and Drug Administration Globalization Act of 2009*, sponsored by Rep. John Dingell (D-MI), is broader, covering drugs, devices, foods and cosmetics. Specific provisions for drug and device safety include:

The scheduling of risk-based inspections depending on the type of compliance history of the facility

Requiring quality risk management plans for establishments

Requiring country of origin labeling; disclosure of source of ingredients

Providing for the potential recall of drugs based on reasonable suspicion of product adulteration or misbranding

Van Trieste said that, PhRMA believes that a strong, well-funded FDA is critical to the health and safety of the American public, and that it is supportive of efforts to provide additional resources to the FDA.

He warned that, "At a time when we are struggling to combat counterfeit drugs and tighten security at our borders, we should be searching for ways to close existing loopholes in the supply chain, and not create new ones by opening up the borders to foreign importers of non-FDA approved drugs, or from facilities that have not been inspected by the FDA."

Regulatory Briefs

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

North America

U.S. FDA Focuses on Strategies to Better Predict, Prevent Economically Motivated Adulteration

The U.S. FDA is developing strategies and standards to better prevent adulteration and counterfeiting within the drug, medical device, cosmetic and food industries. One of those strategies was to hold a public meeting and gather members from the drug, medical device, cosmetic and food industries to discuss their insights into how to best prevent or predict economically motivated adulteration (EMA).

The Economically Motivated Adulteration Public Meeting, held May 1 in College Park, Maryland, focused on how the drug, medical device, cosmetic and food industries, regulatory agencies and other parties can better predict and prevent economically motivated adulteration with a focus on situations that pose the greatest public health risk. The Agency focused on the widespread cases of adulteration that have occurred with heparin, milk products and pet food.

At the meeting, a working definition of Economically Motivated Adulteration (EMA) to bring a common understanding to participants was given. EMA was defined as "the fraudulent, intentional substitution or addition of a substance in a product for the purpose of increasing the apparent value of the product or reducing the cost of its production, i.e., for economic gain."

A *Federal Register* notice, published in April, further defined the new term: "EMA includes dilution of products with increased quantities of an already-present substance (e.g., increasing inactive ingredients of a drug with a resulting reduction in strength of the finished product, or watering down of juice) to the extent that such dilution poses a known or possible health risk to consumers, as well as the addition or substitution of substances in order to mask dilution."

Agency Draft Guidance Document on Pen, Jet and Related Injectors Available

A draft guidance document from the US FDA entitled, Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Product, is available and provides technical and scientific information for sponsors to consider in developing information to support a marketing application for a pen, jet or related injector device intended for use with drugs or biological products.

The marketing application would typically be a premarket notification submission (510(k)) or a premarket approval application for the injector alone. For a combination product that includes the injector, the marketing application would typically be a new drug application or a biological licensing application.

FDA is soliciting comments on the draft guidance; to ensure consideration, please comment on this draft guidance by July 27.

US FDA Draft Guidance on Submission of Bioequivalence Data for ANDAs available

The U.S. FDA is announcing the availability of a draft guidance entitled, Submission of Summary Bioequivalence Data for ANDAs.

The draft guidance is intended to assist abbreviated new drug application (ANDA) applicants in complying with the new requirements in the final rule on the submission of bioequivalence data.

The final rule requires ANDA applicants to submit data from all bioequivalence studies (BE studies) the applicant conducts on a drug product formulation submitted for approval, including both studies that demonstrate and studies that fail to demonstrate that a generic product meets the current bioequivalence criteria. The draft guidance provides recommendations to applicants planning to include BE studies for submission in ANDAs, and is applicable to BE studies conducted during both preapproval and post-approval periods.

The Agency is asking for comments on the draft guidance by July 16, 2009.

U-Report: PDA wants to publish your Regulatory Briefs online and in the *PDA Letter.* Send them to Emily Hough at hough@pda.org and we will consider publishing them.

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NEPDA Feasts on 20 Years of Success, Discusses Container Closure Integrity

Roland G. Bizanek, PhD, Biogen Idec

On March 11 at the Hilton Garden Inn in Burlington, Mass., the PDA New England Chapter (NEPDA) marked its twentieth anniversary with a well-attended meeting on PDA's *Technical Report No. 27, Pharmaceutical Package Integrity.* Representatives from 45 diverse pharmaceutical and medical device companies from the New England area joined to learn from two outstanding experts in their respective fields of container closure integrity testing-**Roger Asselta** and **Heinz Wolf.** Complimentary hors d'oeuvres and drinks were provided during the valuable networking session due to the continued support of our meeting sponsors—Masy Systems, Seidenader, Baxter Healthcare Corporation, Boston Analytical, Genesis Packaging Technologies, Lancaster Laboratories, TSI, and Wilco.

Following the scrumptious dinner, NEPDA President **Jerry Boudreault** called the meeting to order and presented the updated 2009 NEPDA goals for the student chapter:

- Initiate monthly meetings
- Second Meeting: March 25
- Sterilization Technology by **Mike Harrison**
- Student Chapter Field Trip
  Biogen Idec, Cambridge
- Establish Scholarship Program
  Budget Approved, Policy draft circulating
- Strengthen succession process
  Election planned for 2nd quarter 2009

The student chapter of NEPDA is relying on volunteers among our members to present on the topics of Cell Culture, Analytical Chemistry or Stem Cells at the meetings in April, May and September. The sessions will be held at Middlesex Community College in Massachusetts, typically on a weekday from 5-6 p.m. The format will be an open forum in order to minimize the presenter's preparation time and to encourage multiple representatives. The schedule and information will be posted on the NEPDA website http://pdachapters.org/newengland/. PDA members are encouraged to review the schedule and volunteer in advance to attend by contacting Jerry at boudreault@ddres.com, and/or **Maurice Perez** at juanmpz@hotmail.com.

Roger initiated the seminar portion of the March dinner meeting with his presentation entitled, "Test Method for Indirect Measurement of Elastomeric Closure Compression Using an Automated Residual Seal Force Tester." He has been a member of PDA for many years and has been active with the Packaging Science and Lyophilization Interest Groups. He is also a member of the American Society for Quality. He has written and presented previously on several aspects of pharmaceutical container/closure systems. He holds a BS in Biology from Maine's Nasson College and received a certificate in quality management from Penn State. Roger is a Senior Advisor with Genesis Technical Advisors, a consortium of pharmaceutical packaging consultants. Roger started with explaining the necessary definitions using easy to understand visuals, followed by a description of the residual seal force test method and the basic concept of it.

Heinz followed with his presentation on "Non-Destructive Container Closure Integrity Testing." He focused on developing inspection technologies for the packaging industry that perform with a high degree of precision and reliability to simplify testing and validation processes in the food, pharmaceutical, medical device and container industries. Heinz received his Bachelor of Science degree in mechanical engineering from the Ingenieurschule in Bern, Switzerland. He started by describing the generating artificial defects in prefilled syringes, using round robin testing of the ASTM F2338-09, and comparing the method against dye ingress. Next he described airborne ultrasonic technology and its application on tyvek seals.

The program then proceeded into a forum where Roger and Heinz answered application and technical questions from the audience. [**Note:** Please note that Roger's and Heinz's presentations are available at the NEPDA website: http://pdachapters.org/newengland/ and then visit the link for "Presentations."]

The NEPDA encourages you to go to its website, http://pdachapters.org/newengland/, where you can learn of upcoming educational meetings, business meetings, advertising opportunities (sponsorship, newsletters), policies, contact information, and six years of presentations.

PDA's *Who's Who*

Roger Asselta, Vice President, Technical Affairs, Genesis Packaging Technologies

Jerry Boudreault, President, Drug Development Resources, and PDA New England Student Chapter President

Mike Harrison, President, Biotechnicians Network

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

Heinz Wolf, General Manager, Packaging Technologies and Inspection

PDA TOOLS FOR SUCCESS

Rally Your Employees in Tough Times: Point Towards a Better Future

Chris Witt

The economy isn't in the best shape. Maybe you've noticed. Your employees certainly have.

The bad news–job losses, home foreclosures, bankruptcies and a tanking stock market comes, in the words of Shakespeare, not single file but in battalions. And prognostications by economists (how bad will it get? how long will it last?) provide little comfort. "This has translated into less productivity at work," according to a report by CNN, "because of anxieties about salary, heavy workload and job security."

What's a boss to do?

There is no easy answer, no quick fix, no one solution. But business leaders at every level–from CEOs to line managers–can do something to address their employees' worries and to rekindle their motivation. They can give a speech.

A speech in difficult times can be anything from a formal company-wide address to casual remarks at the start of a new shift. But the intent is always the same: to keep employees focused, motivated and working hard.

To make your speech more motivating, follow these guidelines:

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

- **Lead with the facts.** Be as open, honest and forthcoming as possible. Give a complete account of the situation as objectively as you can. If you hold anything back or if you are evasive, you will feed your employees' fear and compromise your credibility.

- **Acknowledge people's feelings.** You don't want to turn your speech into a therapy session, handing out Kleenex and encouraging people to have a good cry. But if you ignore your employees' feelings, they will think that you're out of touch or, worse, that you don't care. Acknowledge their feelings in a general way, using broadly applicable words like *difficulties, worries, concerns, anxieties* or *fears*. Acknowledge what people are feeling and move on. Say, if not in words, then by your empathy, "I care."

- **Interpret the facts.** In spite of what is often said, the facts don't speak for themselves. It's your responsibility as a leader to gather the facts (all the facts), evaluate them, analyze them and come to some understanding of what they mean. And then it's your responsibility to share your understanding with your employees. Just don't tell them, for example, sales have declined 30 percent; tell them what a 30 percent drop in sales means. Help them understand what's going on.

- **Create a positive metaphor.** "Yes, these are tough times," the manager at a defense contracting company told his employees, "but we've been through tough times before. We're battle-tested veterans. We don't give up. And we leave no one behind." That metaphor–battle-tested veterans who don't give up–resonated with his employees and renewed their determination. Be sure that the image you choose is one that you personally believe in and that your employees can adopt.

- **Make hope sensible.** You can't counteract concrete negative images –homes being foreclosed, people losing jobs, businesses closing down–with abstract positive concepts like perseverance, resolve and dedication. If you want people to believe in hope, you have to make it *sensible*, which means according to the dictionary "perceptible by the senses or the mind." The best way to show people images of hope is by telling them stories.

- **Be action oriented.** It's counterproductive at best to say, "You're wrong to think like that" or "You shouldn't feel that way." You can't change how people think or feel–only they can do that–but you can change how they act. And by changing how they act, you create the possibility that they'll change their thoughts and feelings. Almost a century ago William James, the philosopher and psychologist, made an assertion that has been long since been proven: "Actions seem to follow feeling, but really action and feeling go together; and, by regulating the action, which is under the more direct control of the will, we can indirectly regulate the feeling, which is not."

- **Don't go overboard.** This isn't the time–people aren't in the mood– for pep rallies and rah-rah-isn't-everything-great celebrations. Tell anxious people to cheer up and put on a happy face, and they'll be less, not more, likely to do so. Be ebullient, and you'll be unbelievable. Instead, be confident, positive and purposeful.

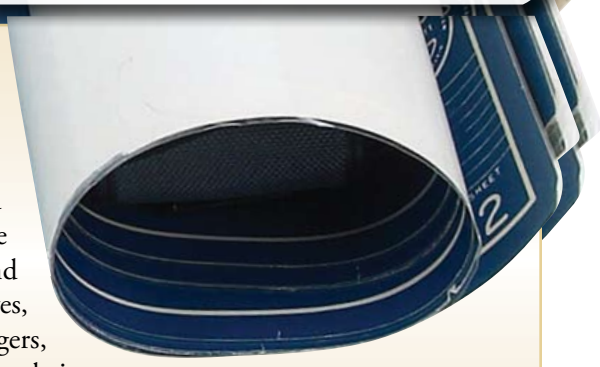
- **Say what *you* want and explain why *they* want it too.** Tell your employees in a short, simple sentence exactly what you want them to do. Then show them how doing what you want will help them achieve what they want. If you want them to work longer or harder or in a different way, you have to figure out how they will benefit from doing so. What's in it for them?

- **"Be the change you wish to see."** The words of Gandhi are as true today in the corporate world as they were 50 years ago in India. Your employees don't simply listen to your words. They filter everything you say through their experience of you. Your actions, attitude and interactions with them are more than an example for them to follow; they are also the lasting message people will take away from your talk.

- **Tell the truth.** Part of why the economy is in such sad shape–not the entire reason, but part of the reason–is because some prominent leaders have been mistaken, unreliable or downright dishonest. People aren't as willing as they once were to take the word of their leaders. You have to prove your trustworthiness. If you say anything that your listeners doubt, they will doubt everything you say.

As a leader, it's part of your job to rally your employees in trying times and point them toward a better future. What better way to do that than with a well-executed speech?

If the challenge of giving such a speech–positive, inspirational *and* truthful–seems overwhelming, consider this: Your employees want you to succeed. They don't want to slog through their days, depressed and anxious. They want you to help them keep hope alive.



About the Author

As an executive speech coach with professional experience, **Chris Witt** of the newly released book, "Real Leaders Don't Do PowerPoint," and founder of Witt Communications. He helps CEOs gain board approval and company-wide support for initiatives, empowers newly promoted managers, helps technical experts simplify their presentations to win multi-million dollar contracts, and enables entrepreneurs to grow their businesses through the power of effective speaking and presenting. For more information about his services, call 619-295-8411 or visit www.wittcom.com.

Volunteer Spotlights

Barbara B. Zinck

President, Zinck Consulting

Education: BS, Chemistry, Muhlenberg College

PDA Join Date: 1993

Areas of PDA Volunteerism: RAQC member 2004-present; Membership Advisory Board member 2008-present; the 2008 and 2009 PDA/FDA meeting planning committee member; 1996, 2004, 2005, and 2007 PDA meeting speaker; 2008 PDA meeting moderator; 2007-2008 PDA comments on Eudralex, Volume 4, Good Manufacturing Practice Draft Annex 2 on Manufacture of Biological Medicinal Product for Human Use committee member; 2008-present PDA Task Force on GMPs for Investigational Medicinal Products Committee Member

Interesting Fact about Yourself: I love volunteering for PDA and professional organizations in addition to volunteering for community and charitable organizations. I gained a whole new perspective on priorities while repairing homes with a youth group in the Appalachia area of Kentucky. When I finally retire, I will probably spend my time volunteering with a goal of overseas mission work.

Why did you join PDA and start to volunteer? I joined PDA based on recommendations from colleagues and started volunteering for PDA for the same reasons. A few years ago I wasn't sure if I could afford to continue my membership, but then I began volunteering and gained (and continue to gain) so many benefits from volunteering. Now I feel I cannot afford to not be a member!

Of your PDA volunteer experiences, which stand out the most? All of the volunteer opportunities are rewarding. It was great fun making a presentation at the 2008 Volunteer luncheon on the top 10 reasons to be a PDA volunteer.

How has volunteering through PDA benefited you professionally? Volunteering for PDA has opened many professional doors of opportunity and expertise in addition to meeting wonderful and valuable colleagues.

Which member benefit do you most look forward to? The *PDA Letter* contains important, timely information.

Which PDA event/training course is your favorite? Every PDA event I have attended has been fantastic, but my favorite is the PDA/FDA Joint Regulatory Meeting.

What would you say to somebody considering PDA membership? PDA is a great organization comprised of talented, experienced and fun colleagues. The only time I ever bowled at midnight was with PDA volunteers and staff—now that's a fun time especially in Budapest. After joining PDA one should look for opportunities to volunteer and the value of your membership will grow exponentially.

Claudia Nardini, PhD

Director, Industrial Development & Research, Kedrion

Education: PhD, Pharmaceutical Chemistry, Pisa University

PDA Join Date: 1999

Areas of PDA Volunteerism: PDA conference speaker; PDA's Italian Chapter Steering Committee member; PDA/EMEA Conference planning committee member (February 2008)

Professional Awards Won: I have received a formal letter of thanks from the government's regulatory agency, Agenzia Italiana del Farmaco acknowledging my support towards the resolution of a rare disease problem. This is something of which I am very proud.

Interesting Fact about Yourself: I like photography, especially in black and white. I often take photos in the hills of Tuscany near my home in Lucca, Italy. The area is very beautiful and lends itself to being photographed. I like to frame my more artistic photos giving them a title from a piece of music that I particularly like.

Why did you join PDA and start to volunteer? I had the opportunity in 1999 to participate with the preparation of the Italian PDA Conference held in Pisa, *Validation and Risk Analysis in the Manufacture of Sterile Pharmaceuticals, Bulk Drugs and Related Health Care Products*. That evolved into the birth of the PDA Italian Chapter which materialized formally in 2000. The enthusiasm shared by me and other colleagues from the Italian pharmaceutical world, together with the support given by Jim Lyda at a pivotal moment for PDA Europe made it very exciting to create the PDA Italy Chapter.

Of your PDA volunteer experiences, which stand out the most? Being a PDA volunteer provides me the chance to network with others in our industry for comparison with other perspectives in the international pharmaceutical world. In this way we can share the common desire to exchange acquired experiences and competences.

How has volunteering through PDA benefited you professionally? I have been working in the plasma protein field for 15 years, holding different positions and gaining experience in worldwide biological companies. I am now involved in industrial development and technology transfer, and am responsible for supervising the activities regarding product safety, including virus/pathogen inactivation or removal and viral risk assessment.

As you might see from my love of photography, I have an artistic soul even though I have a scientific background. I tend to approach my work in this way, combining both qualities. There is a wonderful quote which inspires me in my approach to my professional life, *"The hidden harmony is stronger than the visible one."* This quote from Heraclitus reminds us that true harmony is not restricted to the superficial, but indeed penetrates much more deeply inside the invisible being more important than the visible.

In these times of uncertainty, PDA facilitates the gathering of individuals with differences to create and promote values common to them all.

Along with my growing professional experience, I have found the exchange of ideas and views has helped me to feel more assured in my professional performance knowing that my path is supported by a continual comparison and search for harmony with others in my sector. My involvement with PDA has been invaluable in providing that platform.

Which member benefit do you most look forward to? PDA conferences, training courses and workshops are a resource of information and ideas other than your own. The chance to meet other professionals in my field in order to give me a fresh outlook at what I am currently doing cannot be measured. As has been said, *"The human mind is like a parachute - it functions well only if open!"*

Which PDA event/training course is your favorite? The PDA/FDA Joint Regulatory Conference and the corresponding conference for PDA/EMEA are my two chances each year to step away from my day-to-day work and "talk shop" with colleagues met through these pilgrimages. Also, amongst so many other events, those organized in the areas of Technology Transfer and Pathogen Safety are also favorites.

What would you say to somebody considering PDA membership? In these times of uncertainty, PDA facilitates the gathering of individuals with differences to create and promote values common to them all. Come on and become a PDA member with us if only to enjoy the experience!

PDA Volunteer Spotlights are available online: **www.pda.org/spotlight**

Chapter Contacts

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

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QbD Implementation Knowledge Shared at Delaware Valley Chapter Meeting

Sue Vogt Speth, PDADV Operating Committee Member (Ret. GSK)

Ninety participants from local area pharmaceutical and biopharmaceutical industries attended the PDA Delaware Valley Chapter's 2009 opening meeting series on April 15 at the Desmond Hotel and Conference Center in Malvern, Pa. **Stephen Simmons**, PhD, Vice President, New Product Quality and Process Knowledge, Wyeth, shared his extensive implementation experience with Quality by Design (QbD) in his presentation, "Implementation of Quality by Design – Enabling Real Time Release (RTR)."

RTR is not the goal of QbD. It is a possible outcome of QbD development. Attendees gained an understanding of how Quality by Design offers the opportunity for building a high level of product and process understanding through a science and risk-based approach to development. Stephen described how to successfully implement RTR for a solid oral dosage form developed using quality by design. He explained the use of sampling plans and the statistical concept of batch coverage as determined through operating characteristic curves and Monte Carlo simulations.

He also provided details about the role of risk management tools and their use in establishment of critical and non-critical process and quality parameters and the relationship of Process Analytical Technology (PAT) and Quality by Design. RTR is possible when there is a high level of product and process understanding, a robust control strategy (including PAT), and science and risk-based quality systems aligned with Q10. The concept of "raising the bar" on product quality through QbD and RTR was brought to the forefront along with discussions pertaining to the challenges, opportunities, and benefits of the implementation. At the close of his remarks, Stephen entertained questions and shared ideas with the attendees.

Please Welcome the Following Industry

Jeannine Alexander, Regeneron Pharmaceuticals

Anthony Alleva, TCP Reliable

Anne Altorfer, Boehringer Ingelheim

Irina Avrutsky, Celldex Therapeutics

Anja Bagger, Novo Nordisk

Bert Barbosa, Amylin Pharmacueticals

Susan Beck, Talecris Biotherapeutics

Peter Biedenkopf, Sanofi Pasteur

Stephanie Bourn, Student

Bill Bressler, Amylin Pharmaceuticals

Katja Brinkmann, Gerresheimer Buende

Reagan Broussard, Terumo Medical

John Bundridge, Boehringer Ingelheim

Sharon Chen, Imclone Systems

Shivanthi Chinniah, Amgen

Lars Hoejlund Christensen, Novozymes

Jean Chu, Sanofi Pasteur

Richard Coelho, New England Student Chapter

James Cox, Consultant

Limbani (Bonnie) Custodio, Amgen

Cheryl Dale, DaleBurnham

Tapan Das, Glenmark Generics

Philippe de la Gorce, Nextpharma

Nicolas Degen, Schott Forma Vitrum

Ian Deheegher, Schering-Plough

Tiffany Derrick, GlaxoSmithKline

Weiliang Ding, Abbott

Shrinivas Diwan, Unichem

Kevin Donnewald, APP Pharmaceuticals

Isabelle Ernest, GlaxoSmithKline

Lars Fagrell, Fagrell Consulting

Annika Forss, GE Healthcare

Olga Golubovskaya, Sanofi-Aventis

Diego Gomez, Merck

Joycelyn Gonzales, Gen-Probe

Malene Gron, Pharmakon

Steve Haight, Bausch and Lomb

Eli Harosh, Bio-Technology General (Israel)

Scott Hart, Amylin Pharmaceuticals

Mark Hassett, Unilife Medical Solutions

Kevin Helle, GE Healthcare

Katie Henchir, Biogen Idec

Chikara Hoshino, Tsumura & Co.

Takeshi Iwata, Novartis

Robyn Johnson, Student

Raman K, Microlabs

Edgar Kamantigue, Gen-Probe

Kinya Kariya, Amano Enzyme

William Kennedy, Baxter Healthcare

Rosezetha Keo, Student

Leigh Kimmelman, DeltaTrak

Robert Kirchner, Vical

Philip Kletnieks, Gilead Sciences

Curt Kole, Total Quality

Shinji Kusunoki, Shionogi Analysis Center

Angela Kwong

Mary Lane, Boston Scientific

Nathalie Leduc, Schering-Plough

Richard Lee, Gen-Probe

Des(mond) Lehane, Schering-Plough

Amy Len, Genentech

Irene Lewis, Clarkston Consulting

Robert Lipper, Back Cove Pharma

Anne Loret, LFB BioMedicament

David Lyngholm, Eli Lilly

Erin Ma, Gilead Sciences

Stacey Markovich, APP Pharmaceuticals

Mary Mathieu, Abbott

Erica Mauter, CIMA

Judith Mayer, Mayer Search

Antree McDaniel, Meridian Medical Technologies

Bryan Meehan, Merck

Natalio Mendez, APP Pharmaceuticals

Marie-Christine Misonne, Baxter Healthcare

Stephen Moss, GlaxoSmithKline

Karen Murchison, Aramark Cleanroom

Leaders to the PDA Community

Owen Murray, Lundbeck

Gareth Needham, Bio Products Laboratory

Jack Nijholt, Intervet International

John Nordberg, Baxter Healthcare

Toshio Oda, Seikagaku BioBusiness

Jackson Oh, GlaxoSmithKline

Mohsen Orodpour, AB

Ronald Paradise, Catalent

Pratiksha Parekh, Commissioning Agents

Barbara Peither, Maas & Peither

Fergus Plunkett, Sensitech EMEA

Elizabeth Popp, Lifecore Biomedical

Raffaele Potami, Cold Chain Technologies

William Puent, Lonza Walkersville

DaOnne Pustelnik, Covidien

Una Quigley, NIBRT

Wahida Randecker, Genentech

Kennyth Randle, Alcon Laboratories

Govind Rao, University of Maryland

Harish Ravivarapu, Supergen

Dan Revie, Sanofi-Pasteur

David Ridealgh, Parker Hannifin

Jasmine Riley, Medimmune

Dieter Roethlisberger, F. Hoffmann - La Roche

David Ross, AstraZeneca

Katherine Rossman, Bend Research

Nitin Satav, Millipore

William Scruggs, GlaxoSmithKline

Vishal Sharma, Millipore

Verena Sigmund, Ypsomed

Catherine Simard, Shire

Kenneth Sims, Merck

Monica Skinner, Pfizer

Kimberly Snyder, Genentech

Ung Nak Sohn, LG Life Sciences

Denise Steckel, Genentech

Jochen Stoehr, Intervet International

George Stoy, Bristol-Myers Squibb

Jing Su, University of Toronto

Sherry Tamura, Biogen Idec

Mitsujiro Tanabe, Mitsubishi Tanabe Pharma Factory

Gary Taniguchi, Facet Biotech

Sherry Tegtmeyer, Primary Care Solutions

Michael Tennant, Pfizer

Nicolas Ternest, GlaxoSmithKline

Marci Treadwell, Hospira

Noreen Troccoli, Genzyme

Kenneth Troia, Biotest

Jelena Ursa, PharmEng Technology

Brian Uyeda, Gen-Probe

Marita Vainio, Biotie Therapies

Aad van de Leur, Synthon

Vince Villegas, Genentech

Josh Wages, Sartorius Stedim Systems

Po-Shing Wah, Baxter Healthcare

Steven Walter, MBO Partners

Theresa West, Catalent Pharma

Vinca Widjaja, Abbott

Monika Wiesner, Mycosafe Diagnostics

Alicia Woodfall-Jones, Bulletproof Documentation

Elisa Yee, Hospira

Wu YongFeng, Jilin Province Food and Drug Administration

Feng Zheng, Bayer Healthcare

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

PDA Hosting First Conference on Cell Substrates

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

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

PDA will hold its first workshop on cell substrates used for the production of recombinant therapeutic proteins this summer in Bethesda, Md. The workshop will highlight three areas in which we have seen technological advances that could impact biopharmaceutical product quality and safety. These focus areas are raw materials, virus testing, and new cell lines/cell line engineering. The workshop was designed with the aim of promoting open, robust and productive discussions. To this end, it will culminate with a synthesis session which will be used as an open forum to highlight areas where issues remain unresolved and to identify areas in which consensus may be reached. Discussions from the workshop will be used as a basis for PDA technical reports on cell substrates.

The idea for the workshop arose out of the activities of the PDA Cell Substrate Task Force, which was established to assess what approaches have been taken to address issues, both scientific and regulatory, that have arisen due to technological advances that have occurred subsequent to issuance of previous regulatory guidelines. The importance of this venture is evidenced by the ongoing revisions to chapters of PharmEuropa regarding cell substrates, as well as a revision of the WHO's Technical Report Series, No. 878 on cell substrates. The PDA Cell Substrate Task Force currently consists of 23 members representing industry, regulatory authorities and consultants.

Following a historical overview by **John Petricciani,** MD, Immediate Past President, International Association for Biologicals, on the use of cell substrates for biologics production, the new cell lines session of the workshop will commence with talks on the use of, and safety considerations involved with, the establishment of mammalian cell lines using lentiviral vector gene transfer technology. These talks will be followed by presentations addressing the use of human, insect and avian cell lines as substrates for the production of recombinant therapeutic proteins that include a case study by **Mike Rubino,** PhD, Research Scientist, Elanco Animal Health, Eli Lilly, on the "Full Safety

Testing Requirements For the Approval of A Recombinant Protein Produced in A Human Cell Line." Finally, a United States regulator will address considerations for safety testing of new cell lines. Time has been reserved at the end of the focus area, and all subsequent focus areas, for a question and answer session.

The raw materials portion of the workshop will take place in the afternoon of the first day and will begin with talks on treatment of raw materials to mitigate risk of contamination, including a presentation on UV-C irradiation and High Temperature Short Time media treatment by **Robert Weaver,** PhD, Sr. Scientist, Amgen. This session will then move on to explore experiences in the form of case studies that representatives of industry and consultants have had with the Japanese regulatory authority with regard to raw materials and TSEs. Finally, United States regulators will comment on their perspectives with regard to raw materials and cell line history.

The session on virus testing will occur on the second day of the workshop and includes presentations on new technologies for contaminant detection, case studies on positive test results prior to moving to a couple of talks dealing with compiled historical data of positive virus test results. **Ray Nims,** PhD, Senior Specialist QC, Amgen, will present data on "Adventitious Viruses detected in Biopharmaceutical Bulk Harvest Samples over a Ten-Year Period." Along similar lines, **Hannelore Willkommen,** PhD, President, RBS Consulting, Co-leader of the virus testing working group of the PDA Cell Substrate Task Force, will present results of a task force survey of industry and testing labs regarding *in vitro* and *in vivo* virus testing; in particular the survey addressed, what methods are used, how many positive results have been seen and were these positive results confirmed or false positives. **Sally Baylis,** PhD, Senior Scientist, Paul Ehrlich Institute in Germany, will round out this session with a talk on "Regulatory Expectations for Validation/Qualification of Virus Assays."

Attention exhibitors, PDA is seeking vendors who provide excellent products/services in support of this conference. Space is limited and is on a first-come, first-serve basis. To reserve your space, please contact **Nahid Kiani** at Kiani@pda.org or +1 (301) 656-5900 ext. 128.

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COMPLIANCE OFFICER: ***Basic Requirements:*** Candidates should possess a science degree and specific coursework in an appropriate field of study and professional experience. Candidates with Ph.D. or Master degrees in chemistry, biology, pharmacy, engineering, biochemistry, or a B.S. in one of these areas coupled with substantial industry or inspectional experience, are highly desirable. Basic qualifications required for the above positions, except pharmacy, include: 1) a degree in physical sciences, life sciences, or engineering, which includes 30 semester hours in chemistry, supplemented by coursework in mathematics through differential and integral calculus and at least 6 semester hours of physics, or 2) a combination of education and experience-course work equivalent to a major as described above, plus appropriate experience or additional education. To qualify for higher-graded positions, candidates must have additional amounts of either specialized experience or directly related education. The amount of additional experience or education required depends on the grade of the position. For a pharmacy position, a successful completion of a 5-year course of study leading to a bachelor's or higher degree in pharmacy from an approved pharmacy school, or 1 year of professional pharmacy experience equivalent to at least GS-7, or a 6-year course of study leading to a Doctor of Pharmacy (Pharm.D.); 1 year of professional pharmacy experience equivalent to at least GS-9; or, for research positions, completion of all of the requirements for a master's or equivalent degree in a related scientific field. In addition to a background in those fields, the candidate should have excellent communication skills, both oral and written.

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4th Annual Microbiology Conference Deals with Issues from the Lab Bench to the Manufacturing Floor

Bethesda, Md. • October 5-7 • www.pda.org/microbiology2009

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

As the pharmaceutical industry progresses toward QbD and the use of PAT to control manufacturing processes, the trend has been to relocate analytical procedures from the laboratory bench to the manufacturing floor. In recognition of the critical role that microbiology plays in ensuring the quality of many pharmaceutical products, pharmaceutical microbiology has also followed this path away from the lab bench. Therefore, the program planning committee for *PDA's 4th Annual Global Conference on Pharmaceutical Microbiology* decided that the theme of this year's conference is "Bringing Microbiology to the Manufacturing Floor."

In keeping with the conference theme, the keynote speaker is Professor **Stephen Denyer,** PhD, from Cardiff University in Wales. Professor Denyer's keynote address will be "Pharmaceutical Microbiology – The Move from the Laboratory to the Manufacturing Floor." Professor Denyer is the Head of the Welsh School of Pharmacy at Cardiff University and has published over 150 articles related to his research in microbiology. He has also worked with a number of national bodies including the UK Medical Devices Agency and the British Pharmacopeia. His keynote address will no doubt get the conference off to an exciting start.

Another keynote address will be given at the start of the second day of the conference by **Paul Sturman,** PhD, Industrial Coordinator, Center for Biofilm Engineering, Montana State University. He is an environmental engineer whose work involves biofilm detection and treatment. Sturman will talk about biofilms in pharmaceutical water systems and their survival. His presentation will offer insight on how biofilms form, why they persist and what can be done about them.

As the program planning committee continues their work on the conference agenda, a number of stimulating sessions are taking shape. A session on Mycoplasma testing has been confirmed with three very interesting presentations. **Tony Cundell,** PhD, Director, Pharm. Sci., Schering-Plough, and member of the USP Microbiology and Sterility Assurance Expert Committee, will talk about the new USP General Chapter <63> *Mycoplasma Testing*. **John Duguid,** Staff Scientist II, Genzyme, will give a presentation describing a risk assessment for choosing a rapid mycoplasma test method. Finally, **Barbara Potts,** Director, Genentech, will describe the recent work of the PDA Mycoplasma: Contamination and Control Task Force. The ability to reliably detect mycoplasma contamination and do so in a timely fashion has become extremely important with the rise in biotechnology products.

Additional sessions are being planned for a global compendial update to provide information about new chapters or significant revisions to USP and other compendia. Several members of the USP Microbiology and Sterility Assurance Expert Committee will be present at the conference and opportunities will be available to answer your questions. Representatives from other Pharmacopeia have also been invited to speak. This session will provide an excellent opportunity to hear from the microbiologists who write the Compendial chapters that the industry relies on so heavily.

A session has been planned to discuss endotoxin testing. This session has been crafted to follow the evolution of endotoxin testing from rabbit pyrogen tests to the latest technology designed to support pharmaceutical manufacturing. This session will start with an historic overview of pyrogen/endotoxin testing followed by a presentation about how endotoxin tests are currently performed in the laboratory. The final presentation in the session will be about endotoxin test methods for use on the manufacturing floor.

To give some idea of the flavor of the rest of the conference, speakers have been invited to present talks on such intriguing topics as the Economic Impact of Microbiology; PAT and Microbiology; and Parametric Release for Aseptically Filled Products. PDA also has several task forces working on revising microbiologically significant PDA technical reports. A session will be scheduled to provide updates to three of these technical reports presented by members of the relevant task forces.

Finally, the conference will conclude with an "ask the experts roundtable discussion." A panel of microbiologists representing regulatory agencies, pharmacopeias and industry will be available to answer your questions and engage in discussion among themselves and the attendees. The opportunity to interact with such a diverse group of microbiology experts is sure to be an interesting and educational experience. As Co-chairs of the program planning committee, we look forward to attending the sessions we have just described and learning from the experiences of the speakers and attendees alike.

TRI: Reliable, Renowned and Up-to-Date

James Wamsley, PDA

PDA has long been renowned for the caliber of its publications, particularly its technical reports, which are available as a reliable source of information to improve specific areas such as production, design validation protocols and quality assurance at your company. These global consensus publications are prepared by member-driven task forces comprised of subject matter experts representing industry, academia and regulatory authorities. This level of expertise ensures a broad perspective reflecting best-thinking and practices currently available. One result of these collaborative efforts you may not be familiar with is that technical reports provide many ideas and much of the material for a number of our courses at the PDA Training and Research Institute (TRI).

Our mission at TRI is to establish unprecedented worldwide education, training and applied research in pharmaceutical sciences and associated technologies. Some of the most valuable resources we have to accomplish this mission are the technical reports. We offer three courses at TRI that provide the attendee with training modeled specifically around the information presented in technical reports. The courses were either improved or developed after the publication or revision of one of our technical reports. These courses are:

- "Validating a Steam Sterilizer"
- "Global Regulations and Standards: Influences on Cold Chain Distribution, Packaging Testing and Transport Systems"
- "PDA Technical Training on Technical Report No. 26 (2008 Revision) Sterilizing Filtration of Liquids"

TRI's "Validating a Steam Sterilizer" has been a staple in the PDA course catalog for a number of years. When *PDA Technical Report No. 1, Validation of Moist Heat Sterilization Processes Cycle Design, Development, Qualification and Ongoing Control* was revised and published in 2007, it didn't take anytime at all for **Michael Finger,** Director, Regulatory Affairs, Wyeth and **Donald Drew,** Validation Engineering Manager, Validation Engineering, Abbott, to dissect the material and revamp the course to follow the models outlined in the new revision of this document. Students are now able to learn through lecture and hands-on laboratory training exactly how to perform the procedures outlined in the document. By the end of the training each participant is able to:

- Implement the life cycle approach for the validation of a steam sterilizer
- Design cycle development studies for a variety of sterilization load configurations
- Describe the current United States and EU expectations for the qualification of a steam sterilizer
- Generate and execute validation protocols for their steam sterilizer

By updating this course to follow TR-1, the instructors have brought the document to life, so to speak, and helped ensure this valuable information is put to good use.

Another technical report revised in 2007 has also been a big hit when translated into training course material. The course "Global Regulations and Standards: Influences on Cold Chain Distribution, Packaging Testing and Transport Systems," has been a popular course since it was updated following the revision of *PDA Technical Report No. 39, Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products Through the Transportation.*

The course is taught by two instructors with extensive knowledge in the arena of cold chain distribution—**Rafik H. Bishara,** PhD, PDA and **Tom Pringle,** Acting Technical Director, Tegrant Corporation. Their goal is to make sure each participant understands the concepts and practices of cold chain development and packaging distribution systems. By attending this course, participants will be able to:

- Describe the global practices and regulatory requirements for cold chain distribution compliance
- Explain guidance and regulatory requirements of the manufacturer for distribution and packaging of products
- Identify critical steps to development of profiles for simulation testing
- Describe the distribution environment

By delivering this course several times, in multiple locations around the world, these instructors have helped many people achieve excellence in cold chain distribution, packaging testing and transport systems.

Just last year PDA revised *PDA Technical Report No. 26, Sterilizing Filtration of Liquids* and immediately made this technical report the focus of a new course and highlighted the developments made over the past ten years in the area of sterilizing filtration and their associated technologies. By covering topics such as how filters work, filter selection and sterilization, filter use handling and design considerations, sterilizing filter validation/bacterial retention, integrity testing and single-use disposable systems, students will be able to follow a systematic approach to selecting and validating the most appropriate filter for liquid-sterilizing filtration applications. After initially being offered in the United States, PDA is delivering this course for the first time in China at the *2009 PDA/FDA Asia Pacific Pharmaceutical Ingredient Supply Chain Conference Training Course Series* in June.

By continually updating our courses to include the science and information provided by our task forces, TRI is able to accomplish its mission of establishing unprecedented worldwide education and training.

Upcoming PDA Training and Research Institute Courses

The Next Steps in Aseptic Processing
June 15-19, 2009
Bethesda, Maryland

PDA/FDA Asia Pacific Pharmaceutical Ingredient Supply Chain Conference Training Courses
June 17 - 19, 2009
Shanghai, China

Pharmaceutical and Biopharmaceutical Microbiology 101
July 27 – 31, 2009
Bethesda, Maryland

Fermentation/Cell Culture Technologies Training Workshop
July 28 - 30, 2009
Bethesda, Maryland

Rapid Microbiological Methods
August 3-7, 2009
Bethesda, Maryland

Application of Disposables in Biopharmaceutics
August 25-26, 2009
Bethesda, Maryland Open

Safety Ventilation in Biotech and Pharmaceutical Cleanrooms; Risk Assessment of Airborne Contamination
September 9 -11, 2009
Bethesda, Maryland Open

Developing and Validating a Cleaning and Disinfection Program for Controlled Environments
September 10 -11, 2009
Bethesda, Maryland Open

2009 PDA Regulatory Conference Courses
September 17 – 18, 2009
Washington, DC

Pharmaceutical Water System Microbiology
September 29 - October 1, 2009
Bethesda, Maryland

Fundamentals of D, F, and z Value Analysis
October 5 - 6, 2009
Bethesda, Maryland

Validating a Steam Sterilizer
October 7 - 8, 2009
Bethesda, Maryland

Microbiological Issues in Non-Sterile Manufacturing
October 8, 2009
Bethesda, Maryland

Microbiology of Water in a cGMP Environment
October 8, 2009
Bethesda, Maryland

Environmental Monitoring
October 8, 2009
Bethesda, Maryland

PDA's 4th Annual Global Conference on Pharmaceutical Microbiology Training Courses
October 8, 2009
Bethesda, Maryland

2009 Aseptic Training Session 5
October 12-16 and November 9-13, 2009
Bethesda, Maryland

2009 New Brunswick Course Series
October 19-21, 2009
New Brunswick, New Jersey

3rd Workshop on Mycoplasmas Provided Robust Networking

Barbara J. Potts, PhD, Genentech; Thomas Haemmerle, PhD, Baxter; and Leonard Hayflick, PhD, University of California San Francisco

The PDA third workshop on Mycoplasma held in Berlin on March 24-26 provided a robust networking and educational event for 91 attendees. The Mycoplasma Task Force sub-group leaders reported that the technical report on mycoplasma alternate testing is in final draft form. The filtration sub-group reported on the preliminary *Acholeplasma laidlawii* challenge studies for the 0.2 micron filter with a final goal of developing a standardization of mycoplasma 0.1 micron filter ratings. The peptone and complex media sub-group gave some new insights into the increase in detection of mycoplasma in media fills due to regulatory changes in volume of medium to be tested. This increase in volume and thus sensitivity for the media fills, resulted in a change in how the media was processed moving from heat treatment to 0.1 micron filtration. This resulted in mycoplasma contaminations since these pleomorphic organisms can slip through a 0.1 micron filter.

Multiple speakers lectured about the evidence of biofilm formation with mycoplasmas and an excellent review of biofilm biology was provided by **Hans-Curt Flemming**, PhD, Faculty of Chemistry, University of Duisburg-Essen. The take away message was mycoplasma can form biofilms and mechanical cleaning is the best method to prevent mycoplasmas from reappearing. Feedback from the audience suggested that they want more on biofilms at the next workshop.

Speakers from the EDQM, the U.S. FDA centers for drugs and biologics, and the Paul-Ehrlich-Institut outlined what is expected for nucleic acid detection (NAT) submissions and examples of International Standards developed for viruses that helped to standardize the evaluation of these NAT assays. Multiple NAT assay methods were presented that included touchdown Polymerase Chain Reaction(PCR), PCR and Mass Spectrometry, Quantitative PCR (QPCR) and DNA chip based NAT methods. One speaker on the touchdown PCR method reported on their positive regulatory experience in the EU and Japan. A survey conducted using an audience response system with immediate results shared with participants showed that *A. laidlawii* was the most frequent mycoplasma contaminant found and *Mycoplasma orale* was a close second. It was clear from the survey and the round table discussions that more education on the science of filter rating and cleaning validations should be the focus of the next workshop.

Five poster presenters were chosen at the meeting to give 10 minute oral reviews of their work. One presenter reported that *M. fermentans* and *M.hyorhinis* escaped detection using the routine 28 culture assay and a cell based amplification procedure followed by QPCR, but was then detected with another QPCR and PCR/Mass Spectrometry assay. These isolates were shown to be viable but did not form traditional colonies in the culture assay nor amplify in the cell based assay.

Leonard Hayflick, Professor of Anatomy, University of California, presented information on the Class *Mollicutes* which included, historical reasons for interest; taxonomy and major properties; features that distinguish *Mollicutes* from eubacteria; unusual properties; morphology; cultivation; reproduction; phylogeny; mycoplasma plant ecology; the minimal genome concept; and emerging issues of commercial interest.

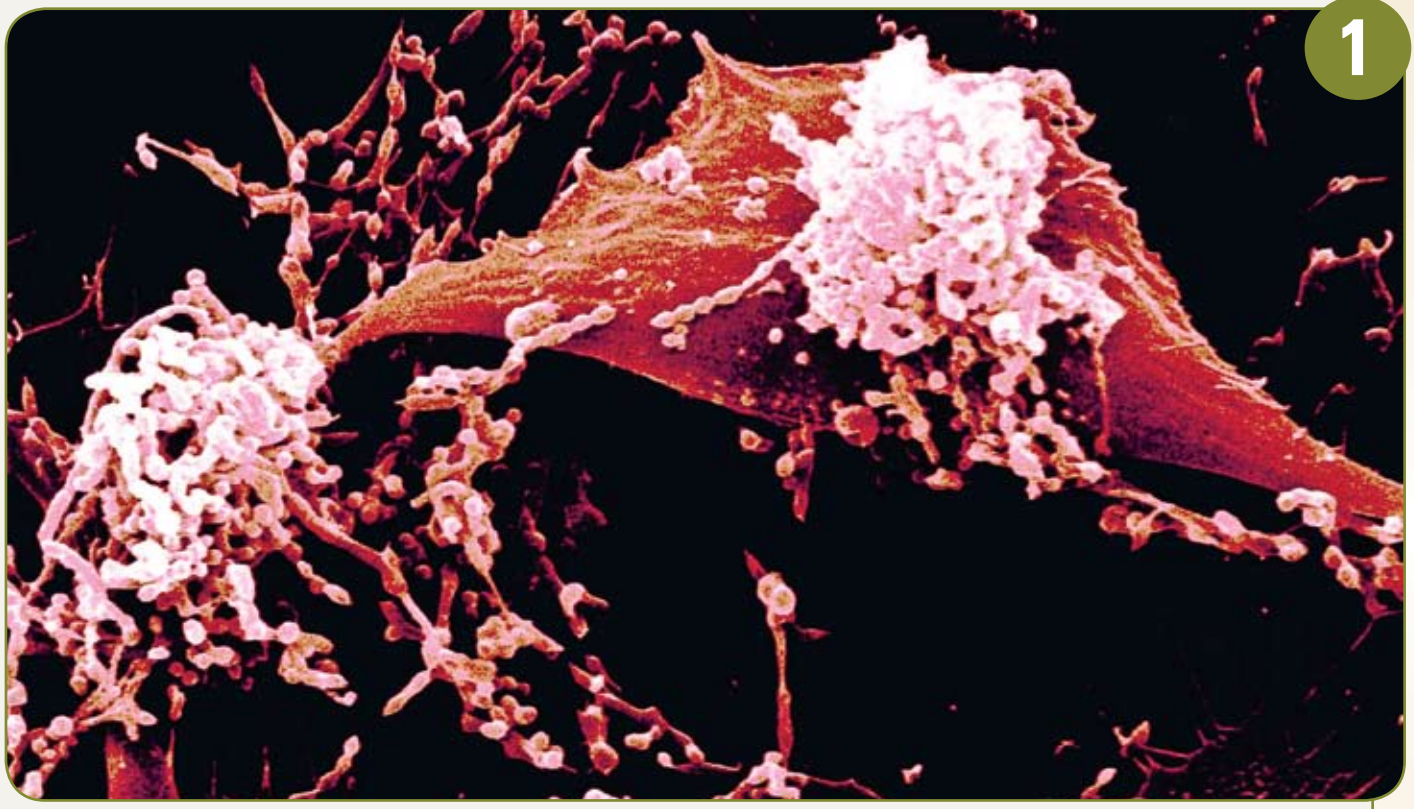
Although illness prevented **Robert Davis**, Research Leader, Molecular Plant Pathology Lab., USDA, from attending, his presentation would have covered the *Spiroplasmas*, a *Mollicutes* Genus that he discovered. They are of importance as contaminants of plants that are becoming a source of nutrients for cultured animal cells. *Spiroplasmas,* unique among the *Mollicutes*, have a spherical morphology, rotary motility, and chemotaxic behavior. Their size is equivalent to a bacterial flagellum. They are found in the gut, hemocoel, and salivary glands of arthropods and are introduced to the phloem sieve cells of plants by sap-sucking insects. Phytoplasmas are the etiological agents of more than 300 different plant "yellows diseases" many of which are of great economic importance causing a multitude of disturbances in plant growth regulation.

Shmuel Razin, Dean, (retired), Hebrew University-Hadassah Medical School, and one of the modern founders of the field highlighted the molecular biology of the mycop lasmas, including his pioneering studies on their membrane biology. He included an outline of current efforts to synthesize the first life form in the laboratory by manipulating the mycoplasma genome which is the smallest of any free living organism.

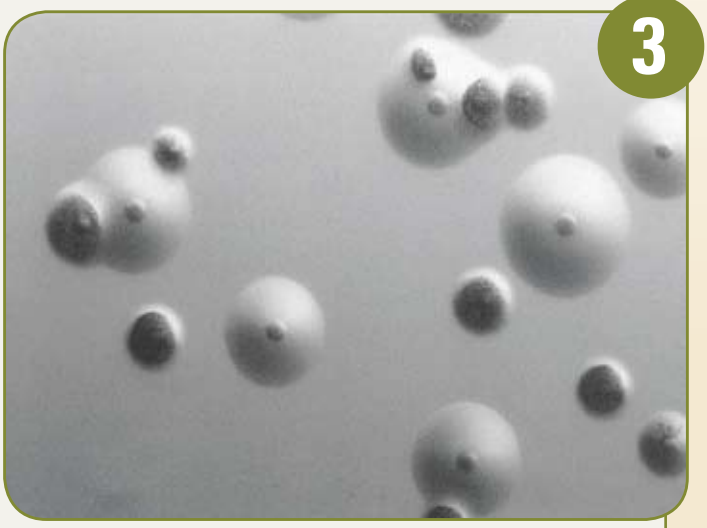
Helena Windsor, Director, Scientific, Mycoplasma Experience, discussed the biology of the Family *Acholeplasmataceae* and, *Acholeplasma laidlawii* in particular, which is one of the five most common cell culture contaminants. Coverage included metabolism, ultrastructure and membrane biology. Emphasis was placed on why *A. laidlawii* is important in the biotech industry because animal serum used in cell cultures is commonly contaminated. Stressed were the different properties exhibited by different isolates and their survival in a wide range of conditions. **Renate Rosengarten,** DVM, PhD, Professor of Bacteriology and Hygiene, Managing Director, Mycosafe Diagnostics, presented strong evidence of biofilms formation with multiple mycoplasma isolates.

Faces and Places

The Third PDA Workshop on Mycoplasma: Best Picture Winners



1. Renate Rosengarten submitted a picture that was taken by scanning an electron micrograph of a mycoplasma-contaminated cell line. This picture won at the Mycoplasma Workshop.



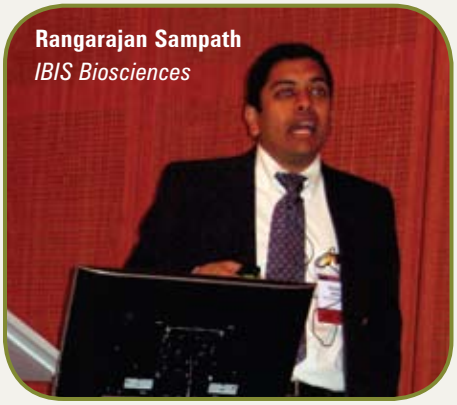
2. Submitted by **Helena and David Windsor.** This picture shows that cell lines can become contaminated with more than one species. (The original sample was diluted to demonstrate different colony morphologies.) This picture came in second at the workshop.

3. Submitted by **Helena and David Windsor,** this picture was created with membrane detection agar inoculated with *Acholeplasma laidlawii.* This picture was given the distinction as coming in third.

Faces and Places

The Third PDA Workshop on Mycoplasma


Barbara Potts, *Genentech;*
Thomas Haemmerle, *Baxter*


Rangarajan Sampath
IBIS Biosciences

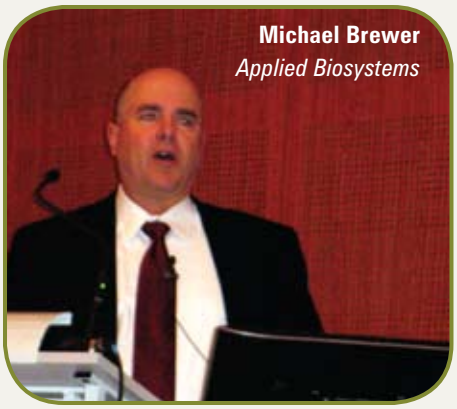

Renate Rosengarten
Mycosafe Diagnostics

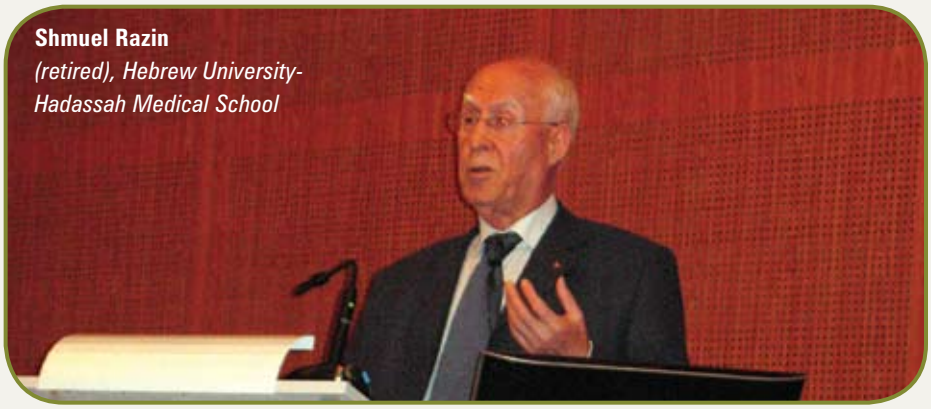

Vladimir Chizhikov
FDA


Markus Klinkicht
Roche Diagnostics

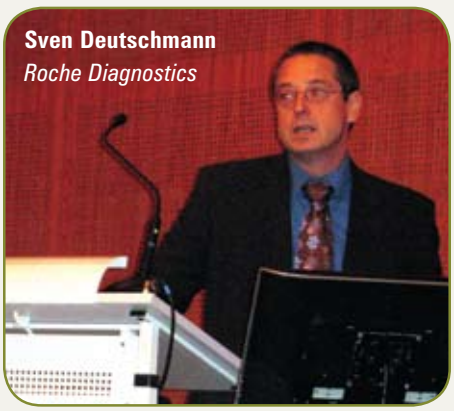

David Asarnow
Bayer


Garry Takle
WuXi App Tec


Michael Brewer
Applied Biosystems


Shmuel Razin
(retired), Hebrew University-Hadassah Medical School


Micha Nübling
Paul-Ehrlich Institut



[**Editor's Note:** PDA would like to thank Russell Nelson and Barbara Potts, Genentech, for taking pictures at the workshop and sharing them with PDA.]

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Ensuring Patient Safety through Supply Chain Control and GMP

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Scientific Planning Committee

Conference co-Chairs: Katrin Nodop, EMEA Inspections Sector; Regine Leo, Inspectorate, Germany; Veronique Davoust, Pfizer

Authorities/Inspectorates: David Cockburn, EMEA Inspections Sector; Vjaceslavs Krauklis, Lativa; Karl-Heinz Menges, Germany; Annie Rietveld, The Netherlands; Ian Thrussell, UK

Industry: Thomas Barthel, Boehringer Ingelheim; Martyn Becker, MB Associates; Anita Derks, F. Hoffmann La-Roche; Liam Murphy, Amgen Ireland; Tesh Patel, Astellas Pharma Europe

13-14 October 2009
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