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PDA Letter

Volume XLIV • Issue #7

www.pda.org/pdaletter

July/August 2008

Risky Business: Aseptic Processing

Walter Morris and Emily Hough, PDA

Few, if any, pharmaceutical processes pose as much risk to the patient as aseptic processing of sterile drug products, a fact PDA members well understand. In one way or another, users of these processes manage risk on a daily basis. With the advent of initiatives by the U.S. FDA, EMEA and other health authorities to integrate risk management concepts to regulatory policy, those responsible for sterile product manufacture and control have been looking to formalize their risk management procedures and are finding even more ways to reduce and eliminate certain risks.

At the *PDA Risk Management and Aseptic Processing Conference,* presentations reviewed various risk tools, offered real-life examples of those tools in practice, and highlighted existing advanced manufacturing techniques that offer true risk-reducing solutions.

The presentations on advanced systems provided the most thought-provoking moments of the conference, particularly the one by former PDA President **James Akers,** PhD, President, Akers, Kennedy & Associates. His overview of advanced methods included video of fully automated, unmanned systems for aseptic processing already in operation. The first example he demonstrated was an aseptic filling line for a positron emission tomography product, the second for an ophthalmic product, and the third for a radiopharmaceutical.

A fourth video showed a "lights-out" (no humans on the floor) advanced isolator filling system for a juice product. This video drew the most reaction from the audience.

Akers offered a sobering alternative reality for these approaches by dissecting the saga of isolator systems starting in the 1990's. He expressed his hope that many of the pitfalls experienced by the early adopters of isolators, which ultimately slowed down their uptake, would be avoided with the technologies of today.

For sure, Akers sees similarities between the push for automation today and the push for isolators over a decade ago: "I think we are moving into an era of aseptic processing that will invite a change," he said. "Perhaps in the same manner or more so compared to what we went through with isolators when we started to convene meetings on isolators about 18 years ago."

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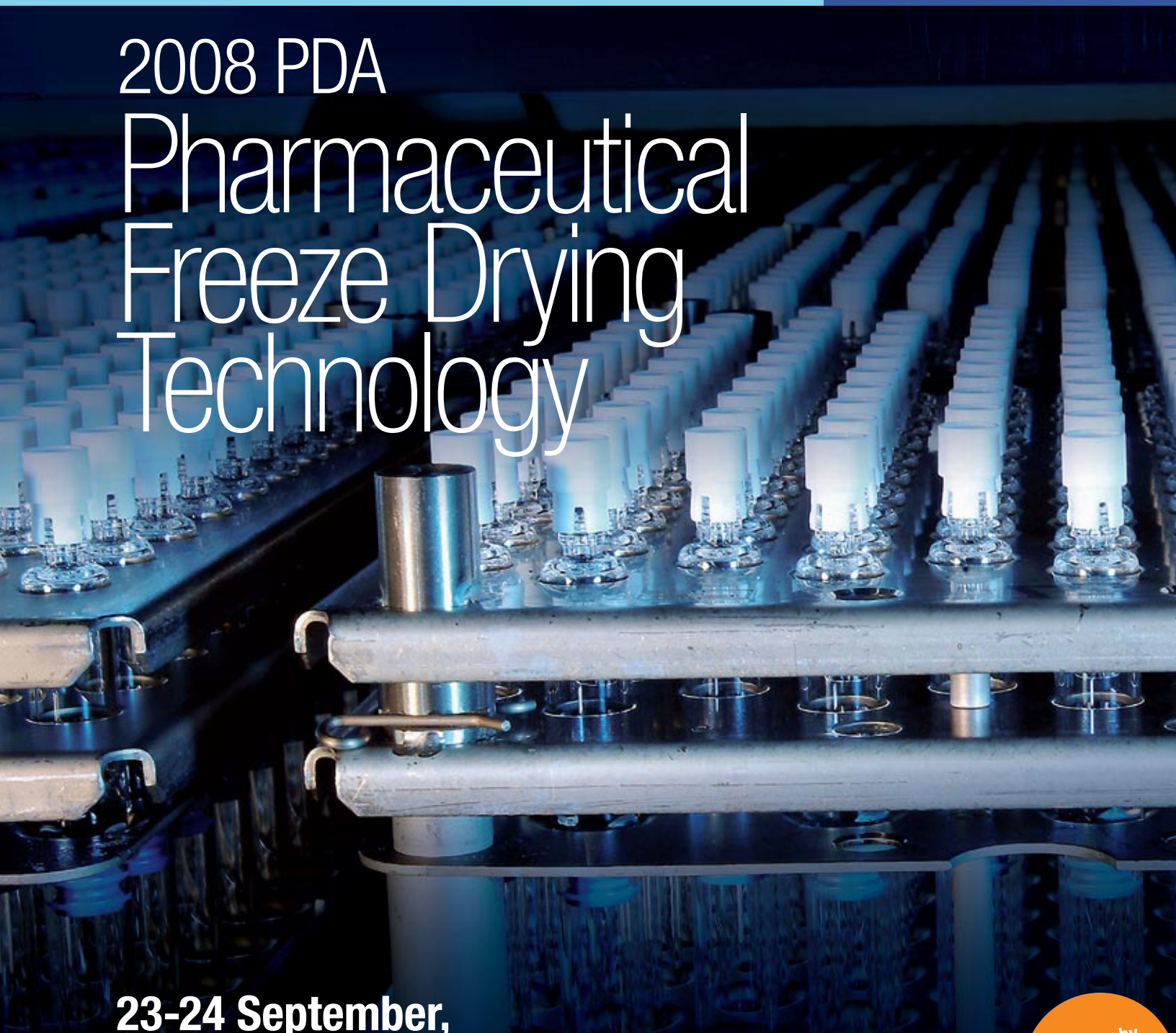

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Robotic arms continue to offer the best approach to separating operators from sterile product. Robotic arm image supplied by Staubli Robotics. Photo collage by James Austin Spangle

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Interview with FDA's Friedman and Uratani on RABS, page 30

Coming Next Issue:
Supply Chain and New Trends in Validation

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Built on the theme, *The Microchip: Impact on the Pharmaceutical/ Biopharmaceutical Industry*, the PDA 2009 Annual Meeting will examine not only today's systems and tools, but also the many exciting future possibilities for the industry – many of which may be of value to your company!

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

Photos courtesy of Bayer Healthcare and Sartorius Stedim Biotech

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Editor's Message

Nifty Number Fifty

This is a special issue for me, being that it is the fiftieth I've worked on since joining PDA in October 2003. I hope readers agree when I say each issue gets better and better! This one, I think, is no exception.

For the past three years, we have dedicated the July/August issue to PDA's core area, which of course is the manufacture of sterile drug products, particularly sterilization science and aseptic processing. We appreciate the timely planning of the PDA *Risk Management and Aseptic Processing Conference* in May which provided us with plenty of material for the cover article, which I co-authored with **Emily Hough.**

On behalf of all of PDA, I want to thank the U.S. FDA for contributing timely, informative and very valuable content for the Quality & Regulatory Snapshot. **Rick Friedman** and **Brenda Uratani** took time out of their overbooked schedules to discuss "RABS Risks and Rewards"—a Health Authority Special Report (p. 30). The 483 observations they shared are a valuable glimpse of how design and operation of a RABS can go wrong. **Tara Gooen** gathered data from recalls to help us figure out what is behind the "lack of sterility assurance" in the Snapshot's Regulatory Trends.

Continuing with the sterile products/aseptic processing theme, **Hal Baseman,** Chair of the PDA Science Advisory Board, shared "A Philosophical Discussion About Media Fills" (p. 10) in the Science & Technology Snapshot, which also includes the Technical Report Watch, a Task Force Corner, an Interest Group Briefing and a PDA Collaboration. Three Sci-Tech Discussion Group samplings this month also touch on pertinent sterile product issues.

We also highlight four member volunteers in Membership Resources, photos from recent events in Programs & Meetings, and the TRI Talk is back with a message from **James Wamsley….** As usual, there is too much great content for me to highlight in this space, so I'll stop here, but I hope you enjoy all the articles in this, my fiftieth issue.

PDA Letter

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Letters to the Editor

We thank those members who have contacted us over the last few months regarding the *PDA Letter.* Readers are always encouraged to contact the editorial staff with your comments, thoughts and concerns.

The April cover story received a lot of attention from readers. Three organizations requested special permission to distribute internally Kristina Spitler's article on training and CAPA. Here is what they had to say:

Dear Editors,

It was with great interest that we read the recent article in PDA Letter entitled "Ensuring T is an Effective Part of CAPA," by Kristina R. Spitler. The article gives an excellent overview of CAPAs (Corrective and Preventative Actions) and takes an interesting look at how firms should examine their tendency to retrain operators as corrective actions to operator errors and deviations when closer analysis might point to a different root cause. It is a thought-provoking read that could benefit all departments and employees, which is why we decided to include it in our company newsletter.

Sincerely,

Laurie Belanger, Covidien

Dear Editors,

Regarding the Article from *PDA Letter* Vol XLIV Issue 4, "Ensuring **T** is an Effective Part of CAPA," I enjoyed this article, reminding us of the importance of **T**raining/ Re-training to ensure effective CAPAs. I look forward to share this article/reminder with my global colleagues. Thank you for your continued support with informative articles.

Best regards,

Leonard Nowak, Schering-Plough

I found the article by Kristina R. Spitler entitled, "Ensuring T is an Effective Part of CAPA" right on the mark. As a Quality Assurance Manager with responsibilities for Quality Analysts (who approve root cause analysis and CAPA activities) as well as managing the site Training Department, I would like to share the information found within this article. Therefore, I am asking permission to make copies for distribution within our site only.

Phillip Baker, Sanofi-Aventis

The January cover story, "Getting to "Preventative" Through Strong Quality Systems," brought this enlightening note from former PDA Director, Stephanie Gray:

Hi Walter,

Just a note about the terminology in the lead article, and use of terms: The regulations use *Preventive,* the New York Times uses *Preventive,* and some people consider *Preventative* a code word. Although preventative is in my dictionary, there are words not to use even if they are in the dictionary; to be considered a reliable source of information, PDA needs to use the proper form, *Preventive.*

Otherwise, I hope you are doing well; I miss seeing you all.

Stephanie Gray, retired

We thank Stephanie for setting the record straight. While the words are synonymous, indeed we understand how extremely important it is to use the proper terms in technical writing.

Emily Hough's first "Tales of the Trail" (March 2008, p. 38), elicited this response from an appreciative PDA Chapter Leader:

Just wanted to tell you how much I enjoyed reading Emily's "Tales of the Trail" in the March 2008 PDA Letter. With so much valuable but dry regulatory and scientific stuff to read daily in our jobs, this was both very well done and very entertaining reading!

And it was a pleasure having her at our PDA Metro meeting. Please come again soon!

Best regards,

Nate Manco, ECO Animal Health and former PDA Metro Chapter President

Correction:

We must correct a mistake we made in the article "On the Horizon: Investigation Medicinal Products in Europe," by Bronwyn Phillips, MHRA. As we were preparing the final proof of the May issue, we had to cut back some articles. In shortening a lengthy author's note to Ms. Phillips's article, we accidently attributed the information therein to a presentation by Hans Smallenbroek, IZG. Ms. Phillips's was citing her own presentation, called "Latest News from the EMEA subgroup of GCP and GMP inspection services."

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Most Significant Contribution to Cold Chain Excellence 2008 Award given to PCCIG

PDA is proud to announce that the International Quality and Productivity Center has awarded the PDA Pharmaceutical Cold Chain Interest Group (PCCIG) with the Most Significant Contribution to Cold Chain Excellence 2008 Award. The award was given in recognition of the published *PDA Technical Report No. 39, Revised 2007, Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products Through the Transportation Environment*. **Rafik Bishara** received an award on behalf of the PCCIG. The PCCIG's collective knowledge, experience and dedicated time to advancing and harmonizing cold chain management practices for pharmaceutical cold chain professionals made this award possible. PDA congratulates all of the interest group members.

TRI and PDA Europe Receive PDA Board Recognition Awards

At the Annual Meeting held in April in Colorado Springs, Colo., the PDA Board of Directors issued "Board Recognition Awards" to PDA's Training Research Institute and PDA's European Office as acknowledgement of significant achievement of both departments in 2007.

Gail Sherman, VP of Education, accepted a plaque on behalf of TRI. The award acclaimed the significant staff achievement of consolidating and upgrading TRI in 2007, as well achieving all operational objectives by the department under challenging circumstances.

Georg Roessling, PhD, Sr. VP of PDA Europe, accepted a plaque on behalf of PDA's European office. The award recognized the establishment of a permanent Berlin office and thriving business in Europe.

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Science & Technology *Snapshot*

A Philosophical Discussion about Media Fills

PDA Science Advisory Board Chair Hal Baseman, ValSource

In January I had the pleasure of attending a meeting of the PDA Irish Chapter in Dublin. The title and focus of the meeting was *Trends in Aseptic Processing – A Risk Management Approach*. The meeting was well organized and hosted by the PDA Ireland Chapter, led by Chapter President, **Frank Hallinan**, PhD, Director, Wyeth, and Secretary, **Paul Logue,** Vice President and General Manager, Elan, and their very capable staff.

The meeting presentations were superb and informative. They included updates on isolators, RABS, facility design, qualification and validation strategies, media fills and risk management. I will not attempt to present summaries of all of the presentations, as I am sure I would misrepresent, omit or otherwise fail to do them justice. **[Editor's Note:** An overview of the PDA Ireland Chapter meeting that took place in February is summarized in the March issue of the *PDA Letter* on page 52.**]**

However, one presentation in particular caught my attention. It was given by **Kris Evans**, formerly from the FDA, and now a Director with Amgen. Evans' presentation was entitled "Process Simulations for New Aseptic Facilities (an ex-regulator's viewpoint)." Evans spoke on the design of process simulation studies. His material was particularly timely, in light of proposed changes to the U.S. GMPs which include a reinforcement of media fills as a component of aseptic process validation.

Validation and the Scientific Method

Evans spent a part of his presentation discussing the scientific method and its role (or at times lack of a role) in current process decision making and validation practice. To quote from his presentation:

> *A scientific theory must be testable. It must be possible in principle to prove it wrong. Experiments are the sole judge of scientific truth. What distinguishes a scientific theory from a non-scientific theory is that a scientific theory must be refutable in principle; a set of circumstances must potentially exist such that if observed it would logically prove the theory wrong.… Science has the problem of induction: No matter how much evidence we have for a conclusion, the conclusion could still conceivably be false. The best we can say is that it is "unlikely" that our conclusion is false when we are using inductive reasoning.…*

Evans acknowledged that he found it easier to present this quote while still at the Agency. Ideally, to achieve true continual improvement, in a manner analogous to the advancement of understanding through the application of the scientific method, we should incorporate this concept into our daily thinking, within reason of course.

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Technical Report *Watch*

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

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

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

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

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

- ***Blow-Fill Seal (BoD)***
- **TR-14 (Revised),** ***Validation of Column-Based Separation Processes (BioAB)***
- **TR-15 (Revised),** ***Validation of Tangential Flow Filtration in a Biopharmaceutical Application (BioAB)***
- **TR-26 (Revised),** ***Sterilizing Filtration of Liquids (BoD)***
- **TR-41,** ***Virus Filtration (BioAB)***

PDA *Collaboration*

Managing Retest Dates on IMPs an Issue for PDA/ISPE Task Team

Emily Hough, PDA

In September 2007, a Task Team was formed by PDA and ISPE to look at alternative methods for managing retest dates for Investigational Medicinal Products (IMPs) utilized in the EU. Made up of eleven members collectively from PDA and ISPE; the core objective of the Task Team is to ensure an efficient process is in place that will help ensure that any IMP dispensed to the patient/volunteer will always be within the authorized shelf-life.

Referencing Annex 13 of Vol. 4 of the EU GMP Guide, the team members believe companies can justify dropping the retest date for IMPs from the package label and instead track the expiry dates through the use of Interactive Voice Response Systems (IVRS) or Interactive Web Recognition Systems (IWRS). Such systems are commonly used by large corporations to manage customer service inquiries via phone or web, and are now employed in clinical trial settings to assist with the randomization of studies.

The Team has identified appropriate processes or technologies (i.e., IVRS) that could be utilized to manage expiry dates; benchmarked and collected data on the current situation; analyzed and understand successes and failures including global trials and challenges; and approached assessors in competent authorities to understand their expectations.

PDA Members:

Volker Eck, PDA
Kathleen Greene, Novartis Pharmaceuticals
Vince Mathews, Eli Lilly, PDA co-lead
Ann McLellan, Boehringer-Ingelheim
Brian Nunnally, Wyeth

ISPE Members:

Michael Arnold, Pfizer
Vincent Devreux, Eli Lilly, ISPE co-lead
Olga Markovskaya, Evidence CPR
Christine Milligan, Fisher Clinical Services
Nicola Mountjoy, Aptuit
Caroline Hickey, AstraZeneca

A follow up with the EMEA and Clinical Trial Facilitation Group was initiated at the PDA/EMEA meeting on the week of February 18 to ensure good reception by the regulators of any proposals. The regulators showed interest in participating and receiving a proposal. **Chris Cullen** of the Irish Medicines Board and chair of the GMP/GCP Working Group, is viewed as the group's EMEA point person.

The team has subsequently mapped out processes for utilizing an IVR or IWR system and for managing retest dates on labels manually (i.e., restricting). Through the use of Quality Risk Management, although appropriate controls can be put in place to appropriately manage retest dates manually, the team has demonstrated that there is inherently less risk associated with the use of an IVR or IWR system.

A proposal, including supporting rationale, for utilizing an IVR or IWR system to manage IMP retest dates has been outlined in a document which will be submitted to the EMEA in the near future for their consideration and comment. In stating the problem, the team explains: "With some exceptions, most IMP retest dates increase in duration and will require adjustment to the dates previously applied to the IMP label." They noted that this process is costly, time consuming and resource intensive, adding that there are some patient safety considerations as well.

The Team estimates that a guidance document for use by both the PDA and ISPE to assist companies who want to utilize an IVRS or IWRS in place of managing expiry or retest dates on IMP labels will be available in the 4th quarter of 2008.

Task Force *Corner*

Task Force Invites TR Review

Sue Schniepp, Schniepp and Associates

Microbiological Data Deviations (MDD) Task Force is pleased to announce that its technical report has reached the global review stage. The report outlines the current best practices for investigating MDDs and explaining why they are different from Out of Specifications investigations. We invite and encourage PDA members to review this report and offer comments and suggestions for improvement. The report is available at https://store.pda.org/review/login.aspx until Aug. 4. The objective of PDA is to offer the membership the most current information in their technical reports. Your contributions will be greatly appreciated.

Interest Group *Briefing*

Prefilled Syringes IG Considers E-beam

On May 27, the European branch of the PDA Prefilled Syringes Interest Group met in Berlin to discuss a number of pressing matters. The bulk of the discussion focused on technologies used to sterilize syringe tubs transferred into the clean room. The focus of the discussion was whether or not electron-beam (e-beam) sterilization provided any more benefits than non e-beam approaches. Experts representing seven companies, both technology enablers and end-users, made their cases, followed by a substantial panel discussion.

The Prefilled Syringes Interest Group plans to continue the dialogue, and its next meeting will take place Dec. 2 to discuss leak testing and siliconization of prefilled syringes.

Recent Sci-Tech Discussions: Acceptance Criteria for Media Fills, Vessel Leak Testing and RO Water (for WFI)—EMEA Position Paper

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.

Acceptance Criteria for Media Fills

Can anybody highlight an acceptance criteria for the media fill?

Respondent 1: See ISO 13408-1.

Respondent 2: My company performs a large number of media fills, and I am sure I can outline to media fill acceptance criteria for you.

The simple answer—as I'm sure you will already know is that you should have zero growth after incubation of the filled units. However a contamination rate of less than 0.1% with a 95% confidence limit is acceptable. A growth promotion test is not specifically requested in either FDA guidance nor EU Annex 1, however both PICS and ISO documentation ask that growth promotion tests are performed. Closure integrity testing can also be performed using the media filled units.

However, in order for me to be able to give you a reasonable simple yet concise answer that you could use, perhaps you could give me a few more details—such as approximate number of units you would expect from a normal batch size, approximate volume of fill, manual or automatic filling? Are you looking at aerobic or anaerobic media fills? Is this an initial process simulation or a re-qualification?

Respondent 3: Refer to Aseptic processing guidelines 2004; see http://www.fda.gov/Cder/guidance/5882fnl.htm.

Respondent 4: Here is, a part of Annex 1 amended (09-2005)of EMEA:

The existing clauses from 5 to 41 are unchanged but re-numbered as 10–46. Clause 47 (formerly clause 42) is changed as follows:

47. Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium. The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst-case situations. Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts. Normally process simulation tests should be repeated twice-a-year-per-shift and process. The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following recommendations apply:

I. When filling fewer than 5000 units, no contaminated units should be detected.

II. When filling 5,000 to 10,000 units:
   1. Contaminated unit should result in an investigation, including consideration of a repeat media fill.
   2. Contaminated units are considered cause for revalidation, following investigation.

III. When filling more than 10,000 units:
   1. Contaminated unit should result in an investigation.
   2. Contaminated units are considered cause for revalidation, following investigation.

Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

Vessel Leak Testing

My company is introducing steel vessels for storage of sterile liquids. These vessels will only be in the order of 100–150 liter volume each. The vessels will not be kept under pressure during use, but before being filled are to be pressure tested by using compressed air or Nitrogen to initially pressurize each vessel which will then be monitored for pressure drop over a set period of time. The vessels/product will be used for European and American Market initially although world wide usage is a final goal. Does anyone know of any rules/regulations or industry norms that are applicable to the test time or pressure drop for such a vessel pressure test? Any help or guidance is appreciated.

Respondent 1: All vessels shall be designed, fabricated, inspected and tested in accordance with the latest edition of following standards: ASME (American Society of Mechanical Engineers) Boiler and Pressure Vessel Code. Vessel Hydtostatic test shall be conducted in accordance with the ASME code section section VIII, Div 1. ➤

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Respondent 2: As far as I know there are no guidances around the pressure drop value. A "significant" drop is not a good sign! But it is a EU requirement to test for bioburden prior to filling. Hope that helps!

Respondent 3: Using 100–150 L pressure vessels for sterile filling is quite a normal practice in some places. Some people now use the pressure tank filling systems. I will not be able to give reference of any norms or regulations, but would like to give my recommendations. In case you do not intend to keep the vessels under pressure of sterile compressed air or Nitrogen, you are only complicating it and taking bigger risks. Still, I would advise you to validate and qualify all your vessels by applying the leak test and pressure hold test methods. Ideally I would recommend 2 times the design pressure and check for the pressure drop over a period that is almost two times the time it is going to carry the sterile product during storage and filling. I would not call it qualified if the pressure drop is more than 1%. Please conduct the pressure hold test at least 3/4 times, before starting actual usage. I would also recommend the vessels to be pressure tested prior to filling the sterile products in the vessels, each time, for a period, it is likely to hold the sterile product. Please ensure that these vessels are under class 100 LAFs in the clean room, once these are filled up with the sterile product.

Respondent 4: As part of our bioreactor sterilization we pressure test prior to performing SIP. The sterilization cycle fails if the test does not pass. At a test pressure higher than the sterilization cycle, the system looks for a pressure drop <0.1 bar guage after 20 minutes. Not the same application as you, but we also want our vessels to be sterile. It's what our manufacturer recommended. I understand that 0.1 bar pressure drop within 30 min is generally accepted. Some use a test 4–5X more sensitive in terms of delta p per minute. However, I have no documentary reference for these data. I would suggest you also integrity test any filters (gas in/out vents) before and after process. Haven't heard of any other criteria and would be interested to hear what other companies do as well.

Questioner: Our people are suggesting a pressure drop of 0.05 bar over 20–30 minutes after pressurization to 1 bar (gauge), but there seems to be no real justification for this apart from being "better" than the 0.1 bar drop which—as you say—seems a rule of thumb measurement. I don't know whether it would be possible to the criteria set out in ISO 10648-2 which really pertains to "containment" systems i.e., isolators, but I suppose it could be argued that both a fermenter and a 100 liter storage vessel are both containment systems. At present we are using steel vessels. There is a proposal to use disposable bag systems in the future—does anyone know if bags are or can "integrity tested" immediately prior to use in the same sort of way the tanks will be?

Respondent 5: One of disposable bags advantage (as suppliers said) is that they don't need air venting filters, as they inflate/collapse as liquid is filled/extracted to/from the bag. The presence of air inside the bag will interfere with liquid extraction (some 3D bags have the extraction connectors in the upper part of the bag and no bottom drain). In our experience, the answer is NO, so you will have to relay in supplier's QA system integrity testing during bags production and your audit and bag's qualification.

Respondent 6: Your citation of "contamination rate of less than 0.1% with a 95% confidence limit is acceptable" for Media Fill is an old guidance. Please refer to Annex 1 of EU GMPs and to Aseptic processing guidelines2004 (http://www.fda.gov/Cder/guidance/5882fnl.htm)for current criteria.

Questioner: [Respondent 5 and all], You may be right! My understanding comes from: The citation, "contamination rate of less than 0.1% with a 95% confidence limit is acceptable" comes from the MHRA *Rules and Guidance for Pharmaceutical Manufacturers and Distributors* 2007. The wording used in the *EC Guide to Good manufacturing Practice Revision to Annex 1*—the current version (came into effect September 2003) (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/revan1vol4_3.pdf) is: "The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth but a contamination rate of less than 0.1% with95% confidence limit is acceptable." A draft version of the EC Guide to GMP Revision to Annex 1—dated September 2004 and not due to come into effect until 1st. March 2009 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/2008_02_12_gmp_annex1.pdf and http://www.fda.gov/Cder/guidance/5882fnl.htm)—uses the same wording as the FDA Guidance you quoted—dated September 2004: "When filling fewer than 5000 units, no contaminated units should be detected. When filling 5,000 to 10,000 units: a) One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill; b) Two (2) contaminated units are considered cause for revalidation, following investigation. When filling more than 10,000 units: a) One (1) contaminated unit should result in an investigation; b) Two (2) contaminated units are considered cause for revalidation, following investigation." So, I suppose it really boils down as to which country you are talking about when you define current criteria. However, wording aside, I am told that both sets of wording actually mean the same thing (apparently you cannot achieve 95% confidence limits with under 10,000 units if you experience

1 or more failures)—one is written in "English," the other in "statistical speak," but are actually the same. So its only the wording that is different, not the acceptance criteria. Right? Over to the group, I would appreciate your thought on this subject.

Respondent 7: A EMEA Annex 1 Amendment is the last current criteria.

Respondent 8: You are correct in that both versions are essentially saying the same thing: one in "statistical speak," and one in plain English. Both the 5,000 minimum and the 3,000 minimum are based on a Poisson distribution with a 95% confidence that the contamination rate is 0.1% or less. The difference is that a 3,000 sample size is accept on 0, reject on 1, while the 5,000 sample size allows you to accept on 1, reject on 2. The larger sample size allows you to accept a run with one contamination event, when appropriate.

RO Water (for WFI)—EMEA Position Paper

After reading EMEA position paper on water for injection prepared by RO http://www.emea.europa.eu/pdfs/vet/qwp/2827108en.pdf, do you agree with some of the assertions pointed out: Biofilms cannot be destroyed? Any attempt by using biocides, temperature, etc. results in a rapid increase in growth following treatment. The net effect is that the RO membrane will become, in practice, a bacterial fermenter. As bacteria in the biofilm grow and metabolize, a range of metabolic by products will be secreted which will include proteins and carbohydrates, some of which may be biologically active. These contaminants are not easily identified and quantified. Of course, EMEA concern is WFI, but several points (all?) render RO technology likely hazardous.

Respondent 1: I find the reflection paper curious to say the least. The statement on "Range of separation for RO" is true for distillation as well, in similar degrees and percentages.

Moreover, a RO has more of a chance to remove "volatile organic chemicals" than a still. If we take at face value the statement that "there are no test methods currently available that would effectively identify all possible toxic contaminants in water" we can close down all our water processing systems including those based on distillation.

The statement that "RO device must be validated to prepare a quality of water identical with water prepared by distillation" is not accurate in my eyes—I would say that the RO device should be validated to prepare a quality of water identical with the EP/USP specifications. Distillation technology is a development of the historical way of production of water, it is the way it was done before RO came of age, distillation was not chosen over RO because it is superior, it just arrived earlier it is not a golden standard.

Microbiological aspects: the paper states that "biofilm formation begins within minutes to grow on RO systems"—the same is true for distillation. If you say that distillation is much better as it is hot then how does that go with "biofilms cannot be destroyed" and "any attempts results in rapid increase in growth following treatment."

These statements are not how the world works, maybe someone should stick there head out of a window?

Distillation is not good if the unit gets gummed up on the inlet with microbiological growth (like RO!) and removes volatile organics poorly at the best even if clean (not like RO!).

In short to understate my opinion, the article is not persuasive at all. Any RO/RO or RO/CDI system that is well designed, operated and maintained can reliably be validated for WFI production according to EP/USP specifications.

Even if I am wrong, and I could be, the "reflection paper" has gone a long way to prove me right.

Respondent 2: [Respondent 1], Unfortunately, this is a document that comes from a body that determines the regulatory status on the issue so it does not matter what people from the industry THINK—there will need to be hard information to refute the stated position.

Respondent 3: Could anybody please post the link to the article?

Respondent 4: Here is the link to the reflection paper on Water for Injection Prepared by Reverse Osmosis. http://www.emea.europa.eu/pdfs/vet/qwp/2827108en.pdf.

Respondent 5: One question from me: If RO is not suitable for generation of WFI based on the 10 points concerning biofilm in the EMEA position paper, why should it be (just) suitable for production of PW (Purified Water)? So far I know, it has never been proven that the liability of biofilm in RO is within the specified limits for PW i.e., 100 CFU/ml, qualifying it is quite OK for PW.

Those 10 points concerning the biofilm looks frightening so as to indicate that RO is a "disaster" for obtaining WFI. Naturally, if biofilm is a disaster for WFI, it should be a disaster for PW as well, unless there is (the so called) well grounded scientific evidence proving that it is not.

Another standpoint, if so (RO "banned" for production of WFI): are injectables produced in the US, deriving its WFI component from RO, prohibited for use in EMEA? To remember that naturally these products are proven sterile by the commonly accepted methods (SAL achieved) whereas the processes are GMP compliant by parametric standards.

Another question: where can I find the US FDA's stringent requirements regarding validation and maintenance of RO?

Respondent 6: Good point [Respondent 5], I also include Highly Purify Water (HPW) also declared by the same EP as a water with same quality as WFI but obtained from another way which is not distillation and by all means with Pharma Applications! So which shall be the that way if RO is practically discarded?

I will save sentences explaining the principles of RO which I think must of us know very well and in my own experience you can obtain WFI quality from it. Though it shall be recognized that from a risk analysis approach RO is more risky than distillation, but not for pointed it as a disaster, and besides distillation is not exempted from being risky neither.

I do not know which would be the proper procedure for addressing EMEA and refuting this paper by specialists in the matter, but I strongly think it shall be done, as if it is stay accepted like that, it will create a big confusion in the industry.

Respondent 7: Hi [Respondent 5], EMEA paper on note for guidance on quality of water for pharmaceutical use considered that purified water can be prepared by distillation, by ion exchange or by any other suitable method, from water that complies with the regulations on water intended for human consumption. In my opinion: any other suitable method mentioned in the EMEA paper would constitute the use of an RO, since the quality attribute of the purified water and its intended use such as non-parenteral non-sterile products can be obtained by the use of an RO; whereas the production of purified water in the USP monograph can be obtained by distillation, ion-exchange treatment, reverse osmosis, or other suitable process.

On the contrary the European Pharmacopoeia requires that WFI must be prepared only by distillation. RO is not considered acceptable in the EEA, where as the USP approved only distillation of an RO for the production of WFI. Despite RO approval all parenteral manufacturers in the USA use water stills for generating WFI. Very few use RO, and most of these manufacturers produce veterinary pharmaceuticals. The consistency of performance provided by RO has been disappointing to those who have tried it and gone back to distilling.

In reality we need some sort of compromise between the two pharmacopoeias where the European Pharmacopoeia recognize directly that purified water can be produced by an RO where as the USP considers that distillation is the appropriate method for producing WFI.

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Modern IT to Breathe Life into Interest Groups

Bob Dana, PDA

PDA has had interest groups for a number of years. The intent of the interest groups was to create an opportunity for PDA members with an interest in a particular topic to come together to explore it, ask questions and get answers and perhaps develop some type of deliverable, such as a technical report. The original plan called for new interest groups to form as the need arose, and to close interest groups as the topic became exhausted.

Some interest groups that were created at the outset of the program are still active and meeting regularly, although in truth not frequently. Others have quietly run their course and have disappeared, while some new ones have come along. For example, a new interest group which will focus on Quality Risk Management was recently formed. This interest group, led by **Mike Long** will be holding its first meeting at the *2008 PDA/FDA Conference* in September. Speaking of new interest groups, we are specifically seeking your input as to whether formation of a new interest group to focus on advanced therapies (tissue engineering, gene therapy, etc.) is appropriate. Another alternate, should this be an area of interest, is to include it within the Biotechnology Interest Group. Your input can be sent to me directly (dana@pda.org).

After operating for some time, a few years ago the interest group program was reviewed and some new wrinkles were added. The existing 18 interest groups were assigned to Sections; with a Section Leader assigned to each. The intent was to develop synergies between the various interest groups in a Section. Each interest group was required to meet at least once a year, and space made available at the PDA Annual and PDA/FDA meetings to allow up to 12 interest groups to meet face-to-face. It all seemed like a good idea at the time. However, in actual practice, it didn't seem to work as well as the planners, including this writer, had hoped.

…with modern communication tools, there seems to be no reason to limit interest groups to one or two meetings a year.

Participating in Interest Groups is a powerful opportunity afforded to PDA members, and it's easier than ever to organize, communicate and contribute using modern IT.

There seemed to be a number of things which impacted the ability to achieve the maximum benefits from the program. Some of these probably should have been obvious to us. Providing an opportunity to meet only once or twice a year certainly didn't do much to encourage continuity and realize some of the benefits of the interest group program. In addition, PDA membership in Europe began to grow and there became a need to provide our European members the opportunity to organize interest groups as well; from that a dual interest group structure arose, with "European" and "North American" interest groups existing side by side, often with little or no communications between them. This structure is counterproductive and doesn't lend itself to maximizing the benefits for our members. In addition to the above, technology has provided great improvements to communicate globally in real time.

There's an old adage—*if it isn't broken, don't fix it.* The corollary to that is—*if it is broken, fix it!* And so fix it we will.

We have already taken some steps to do so. We are aligning the interest group efforts in Europe and North America. Interest groups will have co-leaders, one from Europe and one from North America. We will be communicating plans for meetings, projects and other activities within an interest group to all PDA members who "belong" (more on that later) to the interest group in question, no matter where they are located, and those plans will be coordinated by the co-leaders. There may well be interest group face-to-face meetings which are held in one limited geographic location, which is fine. While it may not be feasible for an interest group member in Washington, D.C. to attend an interest group meeting in Paris, for example; the member in Washington should be aware of the plans for and the outcome

continued on page 21

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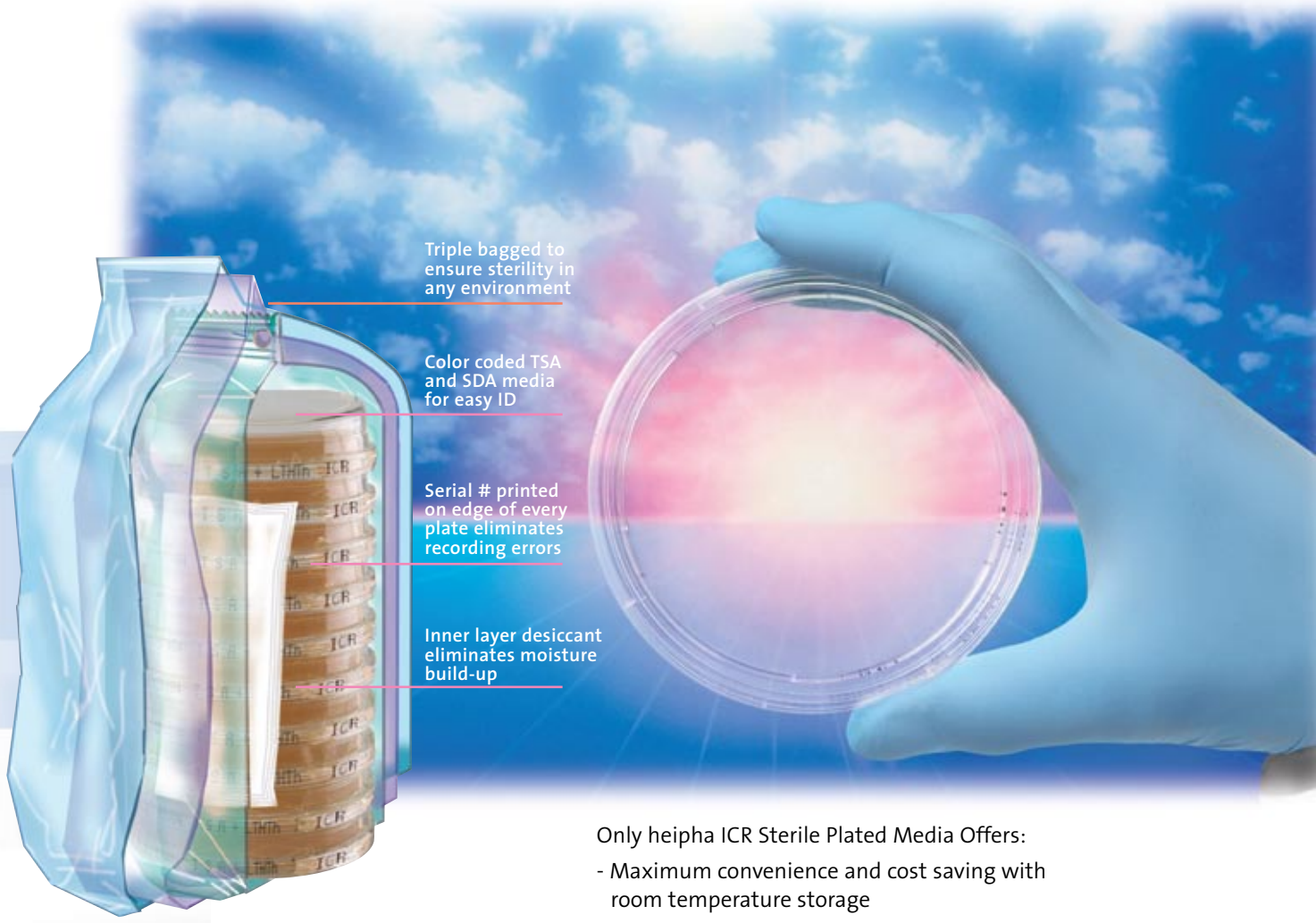

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A Philosophical Discussion about Media Fills, continued from page 10

Evans noted that a key component of a successful scientific method is that we should be trying to prove ourselves wrong as quickly as possible, because only in that way can we find progress. For example, the media fill is a challenge of our aseptic process. It represents an opportunity to uncover weakness in our process in an effort to eliminate or correct these weaknesses. Hopefully, we uncover none and are confident in the process.

Evans went on to list five common errors in the application of the scientific method, among these are: scientist's bias, common sense, background noise, scientific fraud, and shifting paradigms over time. These concepts are particularly relevant to challenging aseptic processes through media fills. Often we start with the strong belief that the process does work. We may *believe* that the filling line can produce sterile product. In fact, *the line must work*, since we have run the line for many years without a problem. And we have witnessed or simulated operational issues/interventions during media fills and have passed those fills; therefore the process is quite robust. We start to think that if we fail the run, then it is probably because of the design of the study, rather than a failure of the process.

Validation and Media Fills

Why do we perform media fill studies? The revision task force behind *Technical Report No.22, Process Simulation Testing for Aseptically Filled Products* has recently circulated a draft version of their report out for public and peer review. One of the key elements of this report emphasizes that while media fills are an important challenge of the aseptic process, and are therefore a valuable component of the overall validation process, they are not the sole means of qualifying the process. In other words, the successful completion of media fill studies alone does not validate the aseptic process unless other factors are considered. These other factors include design and operation of the cleanroom, qualification and validation of the support processes, the training and performance of personnel, and a well defined and practiced quality system

So, should we perform these studies to prove that the process is valid? Or should we perform these studies to learn about our process, perhaps uncover weaknesses and make improvements? If we understood Evans' presentation, the answer is a combination which should certainly include the latter.

…the successful completion of media fill studies alone does not validate the aseptic process unless other factors are considered.

Scientific Method and Design of Media Fills

A few weeks ago, I was part of a presentation on the design of media fill process simulation studies. During the presentation, the question of fill duration was raised. How long should the media fill be?

The FDA states the following in its 2004 Aseptic Processing Guidance, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*:

> *The duration of the media fill run should be determined by the time it takes to incorporate manipulations and interventions, as well as appropriate consideration of the duration of the actual aseptic processing operation….*

The PDA TR-22 Revision Task Force has included this language in its draft report:

> *Process simulations should be of sufficient duration to allow enough containers to be filled to properly determine the contamination rate. The duration should be long enough to stress the process, the supporting environment and the operators….*

Later, I had the opportunity to witness the execution of a set of well prepared media fills. I observed that each operator was walking slowly around the machine with his or her hands in the air as though they were in an operating room movie scene. I should point out that the purpose of these runs was training and the participants were primarily mid-level managers, working in aseptic process operations, but not necessarily in cleanrooms. Nonetheless, their movements were slow, cautious and mechanical. However, there was a definite point during the run, where the participants appeared to drop their mechanical movements and their activities became more "natural." Aseptic technique still appeared to be maintained, but movements were more natural, faster and more production-like. It seemed to occur as a result of the need to drop mechanical, unnatural behavior, in order to successful execute production activities. They appeared to lose inhibitions and the awareness of being observed. This pattern occurred in each run I observed.

If we consider Evans' points on the use of scientific method, then it seems logical that this level of cleanroom activity is what is needed to be captured in the simulation. Capturing the slow, deliberate movements of operators under the watchful eye of observers during a critical process challenge would seem to have limited value when compared with capturing the actual movements and behavior of a production run.

As Evans pointed out to me in Dublin during a post-meeting discussion (over a few pints of Irish ale), an objective

of the media fill simulation should be to uncover problems in the process. In scientific terms, it is a challenge of the hypothesis that our aseptic process is in a state of control, rather than a qualification or demonstration of a known fact. We need to challenge the process to understand its limitations. We need to understand its limitations, to know where it needs to be improved. We need to improve the process to provide better assurance to patients that the products will be safe. The more rigorous the challenge, the more confidence to be gained in the underlying hypothesis (assuming, of course, a successful outcome). A failure does not necessarily refute the hypothesis entirely, but it does obviate the need to improve the hypothesis, or in this case the process, thereby increasing our confidence in future successful challenges.

The identification, assessment, and management of risk should enable us to better understand the limitations of and improve our processes. Media fills are a valuable way to simulate the production process under challenging conditions. While we never want to fail a study—the study should always be designed to obtain as much information about the process as practical and that information should be examined and analyzed with a critical eye.

Evans ended his presentation with this point: Science is the one human activity that seeks ***knowledge*** in an organized way. It's not the knowledge that's organized, it's the ***seeking***.

Over the next year PDA is planning reports and meetings to present and discuss science and risk based approaches to aseptic processing and other related technologies. The objective of these efforts is to provide a forum for an open discussion on the use of risk assessment and management in planning and use of aseptic processing of sterile products. Please plan to join us and participate in this important events and efforts. And perhaps one day we can meet and discuss these ideas (over a pint or two).

Modern IT to Breathe Life into Interest Groups, continued from page 18

of the Paris meeting. While time zone differences can sometimes be a barrier, we will be encouraging global participation in interest group meetings where possible and practical.

In addition, with modern communication tools, there seems to be no reason to limit interest groups to one or two meetings a year. More frequent meetings, some held electronically using tools such as WebEx, should allow more PDA members to take advantage of the benefits interest groups can provide.

These and other plans under consideration should make it easier for interest groups to meet more frequently and should also encourage them to consider developing some type of deliverable, be it a technical report, a meeting, a workshop, etc. Of course, developing deliverables does not preclude a key interest group activity of interacting with other members. The value and benefit of sharing questions, answers and ideas is beyond measure.

Some of these changes should also make it easier for new interest groups to form as needed. Providing the ability for interest groups to meet separately from PDA's major meetings should contribute to this objective. These can only serve to make membership and participation in an interest group more desirable.

That leads to a question which often arises: What do I have to do to become a "member" of an interest group? And what does being a "member" mean? In thinking about the second question first, being a "member" means having the opportunity to contribute to the body of science surrounding a particular topic. It also means the opportunity to achieve benefits not available to "non-members," such as gaining access to discussion forums limited to interest group members. For those of us on the PDA staff, interest group members are an excellent resource for participation on various task forces and program committees, and the interest groups themselves can serve as a breeding ground for new TRI courses and instructors.

Becoming an interest group member is easy. There is currently no additional cost to join an interest group, and there is no limit to the number an individual PDA member can participate in, although there are certainly some practical limitations to that. Ideally, we'd like to see our interest group members actively participating, not just adding their names to another mailing list. To join, just go to the PDA website and complete the membership form.

So that's a bit about our plans for an update to our interest group program. However, we'd love to hear from you, our members, about your thoughts and ideas for the interest groups. What works and what doesn't? What would you like to see in an updated interest group program? What's not important?

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Risky Business: Aseptic Processing, continued from cover

Back then, he said, experts felt the introduction of isolator technology would spark a significant change in paradigm for aseptic processing, so much so, "a whole new way of thinking" would be needed.

"I remember one of the very early conferences that I think several people in this room probably attended, **Carmen Wagner** [now President, Strategic Compliance International] actually showed a short subject movie on managing paradigm shifts," continued Akers. "Unfortunately, I would have to conclude that the perhaps the paradigm shift we were shooting for in the 90's never really came with respect to isolator technology."

Akers identified several reasons for the shortcoming. "We saw an unfortunate side effect of a technology that embodied lower risk actually, in some curious ways, increasing validation requirements and ending up with some really, really long implementation times."

Alternative separative technologies were developed, Akers said, because of "phantom risks" that were identified on the "long and winding" isolator road. "In some ways, trying to go to RABS technology and get away from vapor phased hydrogen peroxide or perceptions of problems we have there, in some respect, may have been a reaction to the validation difficulties that we perceived we were having with isolators."

Conditions More Favorable for New Approaches

Today, the stage is better set for automated, robotic and other advanced approaches, Akers suggested. "Unfortunately, the introduction of the isolator era preceded the notion of risk and science-based regulation by about a decade. I am very hopeful that the fact some of the new innovations are coming in this era of risk and science-based regulation will obviate some of the implementation problems that we saw in the past."

Today, the stage is better set for automated, robotic and other advanced approaches.

Akers outlined a number of "needs" for moving forward with new technologies. "We need to completely revisit what we think is important to measure, because I would venture to say that we are moving into an era in which some of the traditional measurements we do in aseptic processing are going to be of minimal value.

"We need to develop global regulatory policies that are truly risk and science-based and rooted in evidentiary science rather than in conjecture or personal opinion.

"We need to focus on technology, science and engineering rather than paper compliance. And finally, not to belabor a point, but we really need to consider metrology and avoid the suggestion of control standards that are either irrelevant or immeasurable."

Right now, he added, the "pinnacle of current aseptic processing" is what he calls "gloveless" or "intervention-less" isolators. "This is clearly where we are heading. In fact we are not just heading there. I don't want to leave the impression today that when we talk about intervention-free or gloveless aseptic processing, we are talking about something that might occur along about 2020. These systems are in operation today."

In closing, Akers rhetorically asked: "Do we really need to lag 15–20 years behind the technology curve? Is there any really good reason for that? Shouldn't we foster an environment in which moving toward world-leading technologies is considered advantageous, provided it can be demonstrated to reduce risk and perhaps at the same time improve economic efficiencies?"

The U.S. FDA's Rick Friedman expressed optimism about advanced approaches during the final presentation of the conference. The CDER Office of Compliance Director of the Division of Manufacturing and Quality spearheaded the 2004 aseptic processing guidance, which clearly favors the use of advanced technologies.

To Friedman, the decision between a traditional or modern aseptic approach should not be a difficult one to make: "Do you want to use a design approach or install a line that is on the edge of compliance and might not be the 'c' in cGMP in five years? Value engineering says no."

The Agency has now talked about modern sterile manufacturing approaches "since the early 1990s and watched them mature to wide use," he added. ➤

Summary

Risk to Mitigate		Available Solutions
▪ Open Systems	→	Closed Systems
▪ Filtration	→	New Methods
▪ People	→	Robotics
▪ Interventions	→	Better designs
▪ Environment	→	Real time monitor

A major storm is around the corner. Successful companies will batten down the hatches **today** to weather the storm tomorrow.

Amgen's Martin VanTrieste highlighted advanced approaches to common aseptic processing challenges during his presentation "Staying Ahead of the Curve: The Future of Aseptic Processing."

"There has been very consistent communication from FDA that we expect certain major product protection principles to be applied in a contemporary process design."

Friedman highlighted three characteristics of modern systems: separation, automation and testing. "Separation gives you better protection of the product—isolators, and closed RABS.* Automation—the benefit of updating a previously manually oriented operation to one that employs automation shouldn't be underestimated. Testing—using advanced methods and trending for learning and improving."

Rationale for New Technologies Sought

Advanced approaches occupied the attention of conference participants during the final Q&A session. A question was asked about how best to develop a scientific rationale for moving from the current stage over the "edge" to the modern stage.

Friedman cautioned that it is not typical for a specific technology by itself to be singled out as inappropriate. However, industry experiences with robustness of specific process approaches does matter. "Certain past design approaches were shown to present avoidable risk and did not have very good track records," he said. "Those would be considered ones that merit extra scrutiny and could present too much risk to the consumer given the feasible and valuable alternative approaches that are available and affordable now."

Another question dealt with how to set the criterion for moving to a new aseptic processing paradigm—by looking at the actual outcomes of the existing technologies/approaches in use or on the performance capabilities of new technologies/approaches.

In response, Friedman stated that both are relevant. The ultimate goal for the Agency and companies is prevention by "designing quality in" to an operation and "preventing failures and harm." The panelists agreed that this is preferable to reacting to a bad outcome with a marketed production in order to decide an approach may be of questionable robustness. Based on "the wealth of information" and expert opinions in the industry and Agency, the FDA official stated, "There is a new increment that we are striving to reach to provide the level of protection to the consumer that could be attained given today's advances in manufacturing."

For more on RABS, turn to page 30…

Conference Co-Chair **Harold Baseman,** COO, Validation, ValSource, jumped into the discussion: "I would just be cautious linking results and performance as the reason to move forward with innovation and improvement. I'm sure back in the 1800's a horse and buggy was an outstanding way to get from one place to another. It wasn't people that said, 'Well there are problems if you fall off the buggy, that is why we have to produce cars.'" Referring to the videos shown over the course of the meeting, "If anybody who comes away after looking at the demonstrations and isn't a little envious of the types of technologies that are out there, I really cannot understand that."

Akers noted that some attendees at the conference took exception to his earlier characterization of manual filling as passé. "I made a comment yesterday that the sun should be setting or the credits rolling up at the end of the manual filling era, and of course I wasn't talking about conventional cleanroom manufacturing. I was talking about people manually filling into containers. Much to my surprise I actually got three emails last night suggesting that it was inappropriate to say that manual filling should be passé. They weren't successful in convincing me."

Chris Smalley, Director, Compliance Operations, Wyeth, indicated that firms cannot wait for "permission" from the regulators to move forward.

Earlier in the conference, Amgen Quality VP **Martin VanTrieste** outlined a number of business-related reasons for considering technology upgrades. Drawing parallels to the electronics industry which improved processes in the face of cost concerns, copycats, material costs and reliability concerns, VanTrieste noted that the drug industry is confronted with similar issues today. He warned, "A major storm is around the corner. Successful companies will batten down the hatches today to weather the storm tomorrow."

VanTrieste added, "Many of the solutions are right in front of our eyes, but we are reluctant to embrace the future."

A Review of Risk Management Tools

Attendees were also treated to a number of talks that focused not only on the types of risk management/analysis tools available, but also on their strengths and weaknesses.

James Agalloco, President, Agalloco & Associates, spoke about the analysis of the aseptic process risk in his presentation, "Aseptic Processing Risk Assessment: The Simplified Akers-Agalloco Method." The well-publicized [James] Akers-Agalloco method has been promulgated by the two former PDA presidents for several years.

Driving them to devise the model was their view that the absence of measurable factors makes it difficult to apply standard risk analysis methods to aseptic processes. Utilization of these tools without proper measurable risk factors is tantamount to speeding or jumping out of a plane: "We see all these risks, we take some of them either as individuals or companies, and yet we don't know how to evaluate them." Likewise with the risk models, he said.

After careful consideration of these models, Agalloco and Akers determined "none fit," and "these models really don't have the variables that we need to look at aseptic processing."

An example of the problem, he said, is that there is no way to tell "how many microorganisms are truly in the air." He said that the "various recovery ➤

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systems and various air and surface samplers have variable recovery." Uncertainty is evident even in the placement of the recovery system. "If there is only one organism on this entire table, how do we know we tested the right location to find it? The answer is we don't, we can't, we couldn't possibly; so we are always going to have uncertainty in our measurements and thus uncertainly in our determination of risk."

The A-A Method, he asserted, is one focused on what the operator does in the aseptic process. Agalloco quoted recently deceased former FDA official **Hank Avallone** on the risk operators present: "It is useful to assume that the operator is always contaminated while operating in the aseptic area. If the procedures are viewed from this perspective, those practices which are exposing the product to contamination are more easily identifiable."

This insightful 20-year-old quote points to personnel as the risk source and airborne dispersion as the risk route. As such, any operator intervention always increases risk to patients, there is no truly safe intervention, and the perfect intervention is the one that doesn't happen, said Agalloco.

To limit risk, aseptic processes should be designed to eliminate all unnecessary or "corrective interventions" and to reduce and minimize the impact of "inherent interventions"—those integral to the aseptic process every batch.

Today, inherent intervention activities include line set-up, replenishment of components, weight/volume checks/adjustments and environmental monitoring. Examples of corrective interventions include stopper jams, broken/fallen glass, defective container seals, leaks and other mechanical failures requiring manual correction.

Many inherent and corrective interventions can be reduced significantly through automation and careful equipment selection, Agalloco asserted. "Rick Friedman will always say there is no way that you can validate a bad practice. I will extend that a bit, an intervention is always a bad practice. So our real future of aseptic processing is automation."

Baxter Director of Sterility Assurance, **Ed Tidswell,** PhD, also pointed to some weakness with typical risk analysis tools. "I would argue that the contemporary methodologies available to us are perhaps a little bit more constrained by levels of assumption and subjectivity which leads to a level of inexactitude."

…the team identified several areas where routine surface cleaning frequencies could be reduced up to 80%.

Quantitative risk modeling, on the other hand, presents "less or few of those constraints and allows us to swiftly estimate risk from numerous and variable factors giving an output that truly allows us to understand the probability of ingress of microorganisms into a process or product," he said.

Tidswell reviewed a number of reasons why firms should use risk analysis for aseptic processing:

- Improve product protection
- Assure product protection capability
- Assess routine manufacture
- Assist disposition of batches
- Generate environmental monitoring action limits
- Fuse with PAT

A big problem with contemporary risk analysis, according to Tidswell, is the assignment of risk factor values. In his view, risk factors are "defined in arbitrary terms or surrogate descriptors" and achieved by informed opinion. Further, risk factor determinations cannot adequately represent uncertainty or stochasticity.

He pointed to a number of standard environmental and personnel monitoring devices for measuring bioburden that have wide-ranging recovery efficiencies. For instance RODAC "varies hugely between 2–95%"; swab recovery 15–65%; active air sample recovery 40–96%. "Of course, recovery efficiencies depend upon species, strain, their physiological state, the environment, substrate and technique." In addition, "colony forming units do not equate to microorganisms," he said. As such, 1 CFU on a plate means that, "the best we can say is that there is more than 0 bacteria on that plate; it tells us nothing more than that with great certainty."

As another example, Tidswell pointed to the measure of contamination on an operator's hand. "Could you tell me how many colony forming units you'd expect? And the correct answer is that it really does depend." This question represents the "risk factor value dilemma" in that companies know there is uncertainty. "We know what the average is, we know what the mean is, we know what the minimum is, we know what the maximum is." But when assigning the risk factor value for bioburden, "what do you use? Do you use the average? Do you use the mean? The mode? And that [answer] can have severe and significant implications upon your assessment of risk or your interpretation of it."

Quantitative risk modeling, according to Tidswell, has fewer of the constraints found in contemporary risk assessment. He said that quantitative risk modeling and simulation is a structured systematic means for statistically deriving risk. This approach is widely used across many industries, including airlines and nuclear energy, Tidswell pointed out. His slides provide a detail glimpse into the use of a quantitative risk model for bioburden ingress. ➤

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Case Study

The PDA risk management conference also included presentations demonstrating how risk management projects can help companies more efficiently utilize their limited resources.

Tom Genova, PhD, Fellow, Worldwide Quality Services, Global Biologic Supply Chain, presented two examples of the application of risk management to environmental control. His first example utilized the idea of QRM to "right size" established environmental monitoring programs; his second example, incorporated QRM to update a facility cleaning program.

In the first example, a team was put together to look at EM sampling through the risk management lens to see if the company was adequately adding value to and protecting the patient. They divided the work into two phases: areas that are non-processing rooms and areas used for processing. Genova presented the results of the first phase of the project.

The original sample matrix of environmental monitoring was developed in 1999 during the start up of the facility in question. The project team found that samples were collected at 600 individual sites in the non-process areas for a total of 3900 tests per year.

A hazard analysis tool was used to determine if the risk of "right-sizing" the EM program in non-process areas was acceptable. A relative risk ranking tool was used to evaluate the risk of reducing or eliminating individual sampling sites and to identify sites that could be reduced or eliminated.

The analysis led the team to proceed with the exercise and the resulting risk analysis demonstrated redundancy in the EM testing for non-process areas. The recommendation is to reduce testing in these areas by 30%. Now regulatory filing and change control considerations are being dealt with, and the group is beginning the second phase of the project to evaluate EM samples in processing areas.

The second example dealt with an examination of environmental cleaning practices to identify and remove non-value added activities and to "right size" the cleaning practice. Prompting this study was a recent 13% increase in cleaning area.

Utilizing a similar process and a number of risk tools, the team identified several areas where routine surface cleaning frequencies could be reduced up to 80%. These areas included ceilings, walls, doors and floors. They also found non-routine cleaning to be unnecessary, like hood cleaning following power outages.

The impact on resources were many, including:

- 30% reduction in annual labor hours
- 27% reduction of WFI demands
- 75% reduction in waste disposal

In conclusion, Genova stated that QRM provides a structured approach to define data-based solutions to ongoing business needs and facilitates science-based decision making processes. However, QRM does not provide "a quick fix," he cautioned, nor does it preclude the obligation to focus on compliant solutions.

Robot Evolution

Since the *PDA Letter* last reported about the use of robotics in aseptic processing (July/August 2006, p. 24), we've learned of new advances that could make their use even more valuable and effective. Earlier this year, Staubli Robotics announced the development of the first robotic arm designed to withstand the harsh cleaning procedures used in pharmaceutical isolators.

According to Staubli, the robot is crafted with complex surface coatings and is fully encapsulated, allowing it to withstand corrosive vaporized hydrogen peroxide treatments. Moreover, the company claims that the design eliminates "shadow areas," or surfaces on and under the device that are difficult to expose to the VHP "because the robot is deliberately and methodically moved during sterilization," the firm's literature explains.

While robots are already used in pharmaceutical isolators, Staubli's Stericlean robot will last their entire lifetime without the problems associated with the harsh VHP treatments, according to a company spokesman. The specially formulated coatings on the arm protects paint, lip seals at joints protect seals, and lines and connections were engineered inside the machine.

Tests demonstrated that the device can operate at a high speed rate of 200 to 800 units filled per minute. Sanofi-Aventis claims a 100% boost to productivity by installing the six-axis robot on a syringe-filling line at its vaccine plant in Le Trait, France. Sanofi collaborated with Staubli and ATS Automation, Tooling Systems to develop the system.

Quality & Regulatory Snapshot

Health Authority *Special Report*

RABS Risks and Rewards—A Discussion with FDA's Rick Friedman and Brenda Uratani

Walter Morris, PDA

In recent years, Restricted Access Barrier System (RABS) designed and operated under very strict criteria have emerged as the next best separative technology behind isolators. In 2005, a team of experts including representatives from the U.S. FDA outlined such criteria in a RABS definition paper.[1]

Such systems are becoming popular as one way to meet the expectations of the 2004 FDA guidance on aseptic processing. In the document, FDA was crystal clear that design of an aseptic process should "limit the number and complexity of aseptic interventions by personnel" and also aim to close off the aseptic process from the surrounding environment. The guidance provides examples of advanced manufacturing approaches that can help firms meet these objectives. Approaches achieving that objective are referred to by some experts as "advanced aseptic processing."

FDA CDER Office of Compliance official **Rick Friedman** explained how RABS conforming strictly to the RABS definition paper fit into the advanced aseptic processing category:

> "FDA is very interested in seeing firms adopt truly modern, robust technologies that afford a tangible safety benefit to sterile products. Manufacturing modernization is the central objective of FDA's CGMPs for the 21st Century Initiative. As aseptic processing lines become highly automated and achieve a separation of the line from hazards of the external room environment, a firm with large batch sizes (e.g., 100,000 or 500,000 units) should be in good position to begin to responsibly scale back the number of units used for routine media fills, as long as the program is designed carefully to still include routine and non-routine interventions at a representative number. In any case, there is always the balance and need for an appropriate simulation of duration and number of units to provide substantial chance for detecting a contamination vector, and this will be especially scrutinized in any non-isolated aseptic processing operation."

Friedman is the Director of OC's Division of Manufacturing and Product Quality and participated on the RABS definition project. "Manual setup, inconsistent disinfection practices, risky material transfer concepts, and direct critical zone interventions by personnel continue to be among the concern with non-isolated lines," he said.

Friedman stresses that it would be difficult to find other aseptic processing systems in use today that would be equal to a properly conceived and executed isolator. Pointing to the tenets of the aseptic guidance,[2] he noted that shifts are nothing more than an academic issue for isolators because the line is fully isolated from the external environment. Therefore, merging of the two-per-shift-per-line-per-year standard for routine media fills can be merited for isolators such that two shifts could potentially be simulated in single, semi-annual media fills—as long as the media fill is an accurate representation of the process and of adequate size and duration, and uses a rigorous study design.

When it comes to the Agency, there is no debate regarding sterilization of all equipment inside the RABS…

"In contrast, we emphasize that manually-intensive aseptic lines should be qualified by media fills up to and including the actual number of units of the largest production batch," states Friedman. In addition, the two-per-shift-per-line-per-year standard applies for all other non-isolated systems including RABS. Yet, he believes a firm using a true RABS likely would be able to justify a reasonably lower population of units, with the caveat that a significant number is still needed to simulate the people-dependent intricacies and other operational aspects that have potential to introduce contamination into the system.

"This would be an appropriate approach for RABS that are, by design, never opened during operations," adds **Brenda Uratani**, PhD, Senior Compliance Officer in the CDER's DMPQ. "While isolators are currently considered the best system for aseptic processing, *closed* RABS also have a place in the advanced aseptic processing world."

Friedman agrees, noting that, if operated properly, these RABS are the next best thing to isolators. "A number of firms are designing and operating RABS in accordance with the ISPE definition and with great success.

Regulatory *Trends*

Root Cause: Sterility Related Drug Recalls

Recalls pertaining to sterility concerns can be caused by a number of factors. Recently the U.S. FDA compiled the specific reasons for Class II recalls related to drug product sterility concerns in 2006 and 2007. Overall, 17 products were involved in this preliminary analysis. Of these, 7 recalls were the result of "non-sterility" and 10 the result of "lack of sterility assurance."

Non-sterility means a confirmed incidence of microbial contamination occurred. Lack of sterility assurance (LoSA) can occur because a preponderance of cGMP violations cast doubt on product sterility or because of problems found with the products protective packaging.

CGMPs were the underlying reason in 6 of the 10 Class II LoSA recalls in 06–07, and packaging component integrity the case in 4 of the 10.

Tara Gooen, Compliance Officer/Chemical Engineer, Office of Compliance, CDER provided this preliminary data. Gooen worked with **Lynn Torbeck,** Torbeck and Associates to provide the data to PDA. Lynn is examining the root causes for Class I and Class II recalls and is presenting preliminary results from the project at the upcoming PDA/FDA Joint Regulatory Conference.

Several cases have been publicized. For a system to meet the RABS definition, the user would operate their systems with the stipulation of no open door interventions, or if such a rare intervention is allowed to occur under an 'open RABS' paradigm, they stop the batch, document the deviation in detail, and begin anew following disinfection."

On the flip side, FDA has seen some companies operating "pseudo-RABS" under a standard lower than that defined in 2005, where open door interventions are likely to occur during the operation. In such cases, Friedman says, "it is sometimes hard to distinguish that line from a traditional line. Right now, there is a lot of debate whether any "open" RABS can be categorized as advanced aseptic processing."

When it comes to the Agency, there is no debate regarding sterilization of all equipment inside the RABS, and they have cited firms recently for failing to sterilize the stopper hopper. Investigators also have observed companies purporting to have a RABS allowing frequent open door interventions. Regarding the latter, Friedman stresses the importance of robust design and control: "The system is intended to 'design out' the need for any 'open-door interventions' during aseptic processing. "If a company permits opening and closing the doors to the aseptic processing line rather than using the installed gauntlet gloves found in a RABS, then they are more or less operating in the traditional aseptic processing paradigm and media fill expectations would be similar to that used for other traditional lines." See box for recent RABS-related observations.

Company officials should routinely confirm that systems continue to be operated robustly and consistently, according to Friedman. "A company may be operating a line that meets the essence of a RABS at the beginning. If that line starts to have troubles that were not predicted in the original design concept and the firm now needs to begin opening the doors regularly to address the issues, the operating concept can drift such that they no longer have a RABS—they only have a traditional line which has walls around it."

To sum it up, Friedman emphasizes that such cases "only promote confusion and undermine the integrity of the RABS standard for the rest of the industry."

Recent RABS-related FDA 483 Observations

Observation 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed. The stopper bowl and the stopper hopper are not sterilized prior to each production run. The stopper bowls are sanitized with sterile isopropyl alcohol between production runs and are only sterilized when there is a change in manufacturing with different stopper size. The review of the stopper bowl sterilization record reveals that the stopper bowl could be used as long as 39 days before the next steam sterilization.

Observation 2

Production equipment in the critical area (Class 100) of the aseptic filling line was not completely sanitized. Specifically, the back of the pump cover in the filling area, flat surfaces on the platform under the filling line, and the stoppering area were not sprayed with the decontaminating agent.

Observation 3

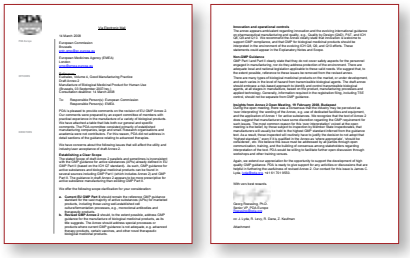
Appropriate written procedures designed to prevent microbiological contamination of sterile drug products have not been established. Specifically, there are no written procedures that describe actions to take when a RABS door is opened on the aseptic filling line to perform an intervention into the Class 100 area. There are no procedures that require the line be cleared of product or that the area be sanitized after the intervention.

References

1. The "Restricted Access Barrier Systems (RABS) for Aseptic Processing *ISPE Definition,*" August 16, 2005, can be found at www.ispe.org by searching RABS.
2. See the FDA *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice,* p. 27.

PDA Comments – ICH Q8r Annex

For the comments grid, visit www.pda.org/regulatorycomments.



Via Electronic Mail

31 May 2008

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Ref: ICH Topic Q8 Annex, Pharmaceutical Development; Annex to Note for Guidance on Pharmaceutical Development (EMEA/CHMP/ICH/518819/2007)

Dear Sir/Madam;

Parenteral Drug Association (PDA) is pleased to provide comments on ICH Topic Q8 Annex, Pharmaceutical Development. PDA is a non-profit international professional association of more than 10,500 member having an interest in the fields of pharmaceutical, biologics, and medical device development, manufacturing and quality.

Our comments were prepared by an expert group of members with practical experience in the area of pharmaceutical/biopharmaceutical development, and are detailed in the attached table. For ease of reference, we have also attached a copy of the Annex with line numbers added.

In addition to our detailed comments we mention the following general points:

• Much of the content of the Annex is a restatement of the parent guideline (ICH Q8, Pharmaceutical Development). It would be helpful to users if the parent guideline and much of the Annex were combined, leaving the actual case studies/examples as the resulting Annex.

• The Annex often suggests that development is either univariate or multivariate. In actual practice, most development activities occur over a continuum, not as an "either/or" approach.

• The general principles described in the Annex apply to biologics and sterile drug products as well as solid dosage forms. However, few examples are provided for these types of products. It would be useful to include illustrative examples for sterile dosage forms.

PDA appreciates the opportunity to support the development of this guidance. Our contact going forward is James Lyda, PDA Europe, lyda@pda.org.

With very best regards,

Georg Roessling, Ph. D.
Senior Vice President, PDA Europe
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Regulatory Briefs

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North America

Amended Device Reporting Rule

The U.S. FDA has published a Direct Final Rule amending the medical device reporting regulations by removing a requirement for baseline reports. The Agency deems it no longer necessary because most of the information is already reported to FDA in individual adverse event reports.

The removal of the requirement will eliminate unnecessary duplication and reduce the reporting burden on manufacturers of medical devices. The rule will be effective October 27 and comments are required to be submitted by August 27.

In the event the FDA receives significant adverse comments on the direct final rule, they will withdraw all or part of it. In the event the Agency withdraws the direct final rule, comments received prior to August 27 will be evaluated under the proposed rule following the normal rule making process.

Europe

EU-U.S. Partnership

At the May 13th Transatlantic Economic Council the work of the European Commission, EMEA and the U.S. FDA on medicines regulation was noted as an example of close and productive collaboration to the benefit of citizens.

According to the European Commission, the EU-U.S. regulatory cooperation will provide opportunities for the simplification and convergence of the two regulatory frameworks.

Currently the types of information that may be shared between the European Union and the United States include, but are not limited to: Drafts of pending laws, regulations, guidance documents, procedures and other technical documents available to the individual participants related to pharmaceutical products; Post-marketing data and information that could have an impact on the public health; Information on quality defect or product recalls of pharmaceutical products known by the FDA to have been manufactured or distributed in the EU, and vice versa; Information contained in or related to marketing or investigational applications for human or animal pharmaceutical products.

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Fax: +1 (847) 296-9312
E-mail: kaipurohit@processtek.net
Web site: www.processtek.net
Contact: Kai Purohit

Kai received his PhD in 1972 from the University of Massachussetts in Food and Biological Process Engineering and has worked under the late Dr. C.R. Stumbo and Dr M. Tung. Kai has also worked under Dr. I.J. Pflug's guidance.

Kai's experience includes (12) years at General Foods and Baxter and industrial consulting for over the past (20) years.

Process Tek specializes in sterilization process engineering, R&D and validation services for optimal aseptic, thermal, chemical, irradiation and non-thermal processes. Kai has special expertise in Bio-Validation, Parametric Release, Process Isolators, HACCP and novel processes for sterile product and package manufacturing, including microwaves, pulse power and high pressure processes, and differential and selective processing. Kai provides technical assistance for validating seal integrity testers, sterilizing heat sensitive and labile products, verifying software and controls for Part 11 compliance, and offers HACCP and GMP audits and training services.

Sterile and Liquids Consulting, LLC

102 Deer Run Ct
Harleysville, PA 19438
Tel: +1 (215) 527-5761
Email: wah81750@comcast.net
Contact: William Hunke, R.Ph, PhD

The development of a new sterile and liquid product requires negotiating a challenging set of tasks. Sterile and Liquids Consulting, LLC (SLC) can help you to make your new sterile or liquid product a reality.

Why add SLC to the job?

- As part of your team, SLC will bring independent expertise to your project. The SLC focus will be on the development of your product, not on the goals of an outside development organization. Helping you develop new products will be SLC's only job.
- SLC knows the development job that needs to be done. SLC has 29+ years of product development experience, and has worked on over 17 different commercial sterile and/or liquid products.
- SLC understands how to anticipate and resolve product development issues. SLC has the experience and expertise to help you with formulation design, clinical manufacturing, late stage development and scale up - all the way through to tech transfer and production.
- SLC can provide expertise to help you assess technology and product opportunities for your new product, or to fuel your future growth.
- SLC can help you to identify the right organizational structure for your operation.

Your decision to engage SLC to support the development of your sterile or liquid product is just smart business. Working with an expert in sterile products and liquids development is simply using the right tools to get the job done as efficiently as possible. Please let SLC provide additional details regarding the consulting services offered.

Tom Bozzo Associates, Inc.

1617 Guston Ct
Silver Spring, MD 20906
Tel: +1 (301) 871-1028
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Email: tombozzo@comcast.net
Website: www.tombozzoassociates.com
Contact: Tom Bozzo

Tom Bozzo Associates, Inc. (TBA) is headed by the former Compliance Director of FDA (CBER) and provides consulting services to the Biologics, Pharmaceutical, Tissue, and Cellular product industries, specializing in compliance audits (Biotech, API, PAI, QA) and corrective action plans (483s, warning letters, license suspensions/revocations, recalls, etc.). FDA's increased emphasis on GMP, GTP and systems compliance means that the regulated industry needs advice it can count on in identifying, preventing and correcting problems. TBA specializes in identifying underlying causes related to observations from internal/external audits or FDA inspection. FDA's enforcement actions and product approval requirements make early resolution of regulatory issues imperative to any business' survival. Tom Bozzo Associates offers experience with sterile products, solid dosage forms, blood products, therapeutics (biotech), vaccines, tissues and cellular products.

Validation Plus, Inc.

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Livingston, NJ 07039
Tel: +1 (866) 760-2483
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Email: jeffreygasman@validationplusinc.com
Website: www.validationplusinc.com
Contact: Jeffrey Gassman

Validation Plus, Inc. has been providing validation plus compliance consulting services to Pharmaceutical, Biotechnology, Medical Device and Tissue Banking firms since 1995. (VPI) will work with your organization to identify requirements and the best solutions to meet your expected outcomes.

Validation Plus focuses on helping build your successful project, and identifying and recommending solutions to your problems.

1. SATISFACTION
   Validation Plus, Inc. is a company with one goal—Your Satisfaction. We have received letters of recommendation from our clients since 1996. Responding to our customers' needs is the most important part of our business.
2. EXPERIENCE
   Our Senior and Principal Consultants come from your industry; most have over ten years of experience. Our Principal Consultants have 20+ years of experience.

Each Validation Plus Senior and Principal Consultant has:

- Hands on experience with multiple validation services and systems.
- Both education and practical experience in their field of validation.

Vectech Pharmaceutical Consultants, Inc.

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Contact: Angela C. Johnson

Vectech Pharmaceutical Consultants, Inc. offers comprehensive consultation and training programs to the pharmaceutical, biotechnology and medical device industries. We provide a full spectrum of services including Microbiology, Rapid Microbiology, Laboratory Issues Contamination Control, Process Optimization, Design, Engineering, Integrated PAT Solutions™, Environmental Monitoring, Biostatistics, epedigree, and Regulatory Affairs. We believe that the most effective way to serve our clients is through a personalized approach, customized to precisely fit the needs of each client

With over 240 years of combined industry experience, our consultants can provide wisdom and turnkey services on time and within your budget. We specialize in providing *comprehensive consulting* and pride ourselves on bringing a regulatory, engineering and scientific perspective to every project. No matter what the job, Vectech will work with you and your staff to achieve the results you expect.

Working Words, Inc.

40 Lloyd Ave., Ste. 307A
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Website: www.workingwords.com
Contact: Rob Miller

For nearly 20 years, we've been helping our pharmaceutical, biopharmaceutical and medical device clients to sharpen critical thinking and technical writing skills, create clear, stand-alone documents and improve compliance and quality. We do this through cGMP consulting and training programs that are completely customized to our clients' documents.

Our customized blended learning programs include:

- Writing Effective Investigation Reports—including RCA and CAPA (English/Spanish version available)
- Precision & Clarity in Technical Reports
- Precision & Clarity in Regulatory Documents
- Writing SOPs That Work
- Root Cause Analysis and Writing for Operators (Spanish version available)

Our cGMP consulting services include:

- Investigation System Remediation (overdue investigations, OOSs, forms, processes)
- CAPA Effectiveness
- Laboratory Systems and Procedures
- Regulatory Documentation and CMC Auditing
- Batch Sheet Revision
- Validation and Change Control
- GMP Auditing and GAP Analyses
- Process Mapping and SOP Remediation
- Documentation Coaching and Mentoring

Analytical Method Validation Training Course Captures Interest at the PDA Japan Chapter

Yoshiaki Hara, Sartorius Stedim Japan and Secretariat of Japan Chapter

On May 13, PDA Japan Chapter held a successful training course called "Analytical Method Validation for Chemical and Microbiological Test." **Kouei Hatada** and **Yoshihiro Ikenaga,** both from Sumika Chemical Analysis Service taught the course.

The PDA Japan Chapter planned this training course based upon several evaluation results from previous courses. The course included technically derived presentations based on actual case studies. The section of the course by Kouei from the chemical analytical approach gave the regulatory requirements of method validation and points to consider when establishing method validation. Yoshihiro's section covered two case studies about endotoxin test method validation and sterility test method validation from a microbiological point of view.

About 160 professionals, including 20 local GMP investigators, participated in the course. During the course, there were many questions from participants. Following the course, 76% of the participants indicated the course was "good" on their evaluation forms. The regulators also said that they appreciated the course.

The PDA Japan Chapter strives to enhance our courses and to contribute both to members and regulators careers.

Are You A New Member? Enjoy Breakfast with PDA in September!

Welcome new PDA members! If you joined PDA on or after April 1, 2008, you are invited to kick-start your PDA membership by attending this year's New Member Breakfast hosted on-site at the *2008 PDA/FDA Joint Regulatory Conference*. This is a wonderful opportunity to learn more about PDA and to meet other new PDA members, board members and staff.

Please RSVP before August 22 by emailing info@pda.org. For questions or to reserve call Hassana Howe at +1 (301) 656-5900 ext. 119.

Stephen Leung, Contec, on the New Member Breakfast:
"As a newcomer to the pharmaceutical industry, PDA has truly helped me develop my industry skills and background information, while also providing me with networking events to meet my professional colleagues. For me, attending the New Member Breakfast was both very interesting and helpful in getting me connected—the food was even top-notch! I'd recommend participating in this event if you've just joined PDA."

2008 PDA/FDA Joint Regulatory Conference

September 8-12, 2008 | Washington, D.C.

PDA Parenteral Drug Association

FDA

www.pda.org/pdafda2008

Recommended Reading

PDA-DHI Publications:

Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing
By Destin A. LeBlanc
Item No. 17253, PDA Member $240, Nonmember $299

Confronting Variability: A Framework for Risk Assessment
Edited by Richard Prince, PhD and Diane Petitti
Item No. 17244, PDA Member $255, Nonmember $319

GMP in Practice: Regulatory Expectations for the Pharmaceutical Industry, Third Edition
By James L. Vesper
Item No. 17199, PDA Member $130, Nonmember $159

Risk Assessment and Risk Management in the Pharmaceutical Industry: Clear and Simple
By James L. Vesper
Item No. 17219, PDA Member $235, Nonmember $289

Systems-Based Inspection for Pharmaceutical Manufacturers
Edited by Jeanne Moldenhauer, PhD
Item No. 17243, PDA Member $255, Nonmember $319

Validation of Analytical Methods for Biopharmaceuticals: A Guide to Risk-Based Validation and Implementation Strategies
By Stephan O. Krause
Item No. 17264, PDA Member $255, Nonmember $315

PDA Technical Report:

PDA Technical Report No. 44, Quality Risk Management for Aseptic Processes - *New*
Item No. 01044, PDA Member $150, Nonmember $250

10% Off *plus free shipping*

when you purchase any PDA publications of $100 or more at the PDA Bookstore during 2008 PDA/FDA Joint Regulatory Conference.

www.pda.org/bookstore

Tel:+1 (301) 656-5900 | Fax:+1 (301) 986-1361

Please Welcome the Following Industry

John Alberts, Pepperdine

Christopher Albright, Wyeth

Jamie Altmann, SPL

Claudia Alzate, Nycomed US

Carmen Amador, Wyeth-Ayerst Lederle

Courtney Anderson, Coalesce

Eilon Asculai, Mediwound

David Bach, Scientific Products & Systems

Arna Baekkedal, Nycomed Pharma

Javier Ballesteros Cherp, Tpro

Franco Bambi, L' Azienda Ospedaliero-Universitaria Meyer

Shannon Bearpark, Shire Pharmaceuticals

Melissa Bebb, Novartis Vaccines

Brandy Benedetto, Sanofi Pasteur

William Bennett, Bennett Consultants

Andrew Berg, Genentech

Jesse Bergevin, Genentech

Aashish Bhatia, Bayer

Barbara Boerger, Monsanto

Ulrich Braeutigam, Sartorius Stedim Biotech

Miriam Briotti, Baxter

Jacqueline Britto, Alexion Pharmaceuticals

Jason Brown, Bausch & Lomb

Jason Brown, Covidien

Khanh Bui, PSCC

Michael Bush, Genentech

Deborah Campbell, Quality & Compliance Services

Peter Cannon, Schwarz Pharma

Debbie Carew, Canadian Blood Services

Helene Castonguay, Bioniche Life Sciences

Robert Chamberlain, Genzyme

Kok-Kaung Chantha, SNC-Lavalin Pharma

Norm Cheale, PharmOut Pty

Jimmy Chen, Bayer Healthcare

Bunkim Chokshi, Genentech

Hing Chong, Health Canada

Hang Chu, Validation Technologies

Phil Clark, Ivensys Validation Technologies

Jacob Cohen, Regeneron Pharmaceuticals

Jeffrey Connell, Dakota Systems

Leah Coppinger, Boston Scientific

Stephan Croft, Allergan

Matthew Daley, Millipore

Wesley Daughtridge, Pioneer Surgical Orthobiologics

Thomas De Beer, Ghent University

Michelle DeCrosta, Discovery Labs

Pranav Desai, Lonza Biologics

Janke Dittmer, Philips

Andrew Donnelly, MedImmune

Stacy Droste, Scientific Protein Labs

Kojo Dwumfuoh, Bayer

Andrew Erickson, Baxter

Christine Errin, Johnson and Johnson

Roger Evans, Vertex Pharmaceuticals

Katherine Ezis, Merck

Mauro Faccio, EZEM

Cheryl Filippone, Baxter Healthcare

Martin Flauger, Boehringer Ingelheim Pharma

Theresa Flores, Novartis

Rachel Fountain, Genzyme

Mark Frankcom, Yellowscape Consulting

Shirley Gallaugher, SteriMax

Mandy Gervasio, Genzyme

Vickie Giacomazza, Ben Venue Laboratories

Molly Gleizes, Columbia Analytical Services

William Godfrey, Baxter Healthcare Corporation

Christopher Goodwin, Talecris Biotherapeutics

Rhianna Goolsby, Lonza

Kimberly Griffin, Pall

Frida Grynspen, Gamida Cell

Dawn Hamil, Ben Venue Laboratories

Jason Hamilton, Fort Dodge Animal Health

Hiroshi Harada, Dainippon Sumitomo Pharma

Daniel Hatton, Parnell Laboratories

Gabi Hazan, Rafa Laboratories

Martin Heavner, EduQuest

Kim Hebert, Ikaria

Andrew Hecht, World Courier

Jun Hirata, Chiyoda

Hanna Hirch, Rafa Laboratories

Irwin Hirsh, Novo Nordisk

Karen Ho, Amgen

Jessica Hoffman, Pfizer

Hal Hopkins, Abbott Laboratories

Robert Hormes, Schott Schweiz

Leaders to the PDA Community

Susan Hotham, Lyophilization Technology

Christopher House, Argos Translations

Akemi Ishikawa, Kissei Comtec

Asa Jonsson, Validation & Inspection Europe

Brian Jackson, sanofi pasteur

Nichole Johnson, Catalent Pharma Solutions

Morrisa Jones, Lyophilization Technology

Yoshinari Kaoru, Sepa-Sigma

Tomoyuki Kawata, Taisho Pharmaceutical

Joshua Keenan, Pacific Validation

Suzanne Kiani, Genentech

Jae-Chul Kim, Estechpharma

Hubert Kluetsch, GEA Lyophil GmbH

Charles Koch, AcuTemp Thermal Systems

Wes Kuhne, Allergan

Mahesh Kulkarni, Biological E Limited

Lawale Ladebo, Ladoke Akintola Teaching Hospital

Karen Lange, VWR International

Joshua Lange, Perimeter Resources

Zoltan Langosco, Biotrace Microsafe

James Laprad, Lonza

Johanna Laurila, AstraZeneca

Sophie Lebel-Binay, BioAlliance Pharma

Gino Lefevere, Stexcon

Robert Lemmon, Intarcia Therapeutics

Lee Levin, Genentech

Micki Lew, United Therapeutics

Ming Li, Baxter

Erica Liang, Bayer Healthcare Pharmaceutical

Kim Lim, Ultimate Labs

Harry Lindenmuth, Lyophilization Technology

Maria Linzmayer, Merck

David Loar, Catalent Pharma Solutions

Renato Lorenzi, Millipore

Bryan MacDiarmid, Student

Anthony Macolino, Imclone Systems

Janet Magar, Rafa Laboratories

Liat Marciano, Rafa Laboratories

Maria Marforio, Tetra Pak

Sam Matthews, Amsino Medical

Penny McCarver, FDA

Enrique Mejias, Wyeth Consumer

Terri Melvin, GXP Institute

Luis Mercado, HollisterSteir

Curt Merideth, Fleming Pharmaceuticals

Paul Michel, S3Pharma

Greg Miles, Medarex

Robert Mills, W. L. Gore & Associates

Allan Mohepat, SPG

Luisa Montanari, University of Milan

Una Moore, IMB Irish Medicines Board

Mark Morgan, Sanofi Pasteur

Brooke Morgan, Amylin Pharmaceuticals

Justin Moscoso, Vitrolife

Stephen Mottola, A&P

Sreekant Nadkarni, FibroGen

Hitoshi Nakayama, Ishihara Sangyo Kaisha

Khushboo Nangia, Centocor

Gary Nappo, Nycomed

Gregory Naugle, Amgen

Gerald Nicklas, Acambis Inc

Andreas Nuhn, Carpus Process Experten

Masaharu Numao, Taisho Pharmaceutical

Zubeda Nuri, Acambis

John O'Donnell, SP Industries

Marcus O'Dwyer, CSL Limited

Ian O'Reilly, Wyeth Biotech

Henrik Oberle, Vetter Pharma-Fertigung

Olaniyi Olaleye, German Friendship Specialist Clinics

Halina Orzel, Catalent Pharma Solutions

Tomoyoshi Osada, Guerbet Japan K.K.

Maria-Antonia Otero, Galax

Robert Otterlei, Sweco

Denise Otto, Imclone Systems

Annie Ouellet, EZEM Canada

Jerry Paciorek, Commissioning Agents

Giuseppe Paganini, Millipore

Paolo Pagliarini, Procomac

Rinesh Palkhiwala, Amerifit Pharma.

Michele Parker, Purdue Pharmaceuticals

Peirani Pascal, Pall

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

Please Welcome the Following Industry Leaders to the PDA Community

continued from previous page

Lalit Patro, M/S Macleods Pharma

Amanda Peter, Quintiles GDRU

Nicholas Petitte, Commissioning Agents

Ann Philippon, Amgen

Luca Pionni, Licosa

Orly Piter, Rafa Laboratories

Phillip Pontikos, FDA

Siva Reddy PV, Trident Life Sciences

Keiran Ragas, CSL

Jessica Ralyn, Mentor Biologics

Scott Ramsay, Sanofi Pasteur

Meliana Ratna, Genentech

Nancy Reinhold, Merck

Brett Richardson, Genzyme

Juan Rivas, Janssen-Cilag

Jean Rivera, Kinetic Search

Mark Roberge, Hollister-Stier Laboratories

Elaine Rodrigues, Lonza Walkersville

Susan Rolih, Meridian Bioscience

Anna-Kristin Rolstad, Norwegian Medicines Agency

Agnes Roque, Baxter Bioscience

Sergi Roura, Grifols Engineering

Malgorzata Rzepka, Lloyds Pharmacy

Hiroki Saitou, Taikisha

Gil Salud, Biologics Consulting Group

Christian Schmidt, Noxxon Pharma

Jonathan Schmidt, Sanofi Pasteur

Benjamin Schultze, PDL BioPharma

Spencer Scott, IT&E International

Joliot See, Hospira

Kaiyu Shan, Dey

Susan Shannon, AstraZeneca

Hiroki Shigematsu, Asahi Kasei Pharma

Rachel Shimonovitz, Rafa Laboratories

Dima Shmarkov, Rafa Laboratories

Rita Silva, Pfizer

Ja Skrzypczak, Hoffman-La Roche

Gregory Slaybaugh, Sanofi Aventis

Jonah Smith, CSL

Andrew Smith, Lyophilization Technology

Stephen Smith, Boehringer Ingelheim Vetmedica

Leonard Smyth, Invensys

Alberto Soto, Wyeth Consumer

Chris Stevens, Bristol-Myers Squibb

Laura Stevenson, Sanofi Pasteur

Bradley Storms, Cook Pharmica

Michelle Stutelberg, Fluid Flow

Mick Sutherland, CSL Biotherapies

Yoshiaki Suzuki, Toyama Chemical

Ilana swisa, Rafa Laboratories

Steven Tackach, Sanofi Aventis

Gigi Taylor, CorePharma

Matthew Teli, Shire

Steve Thomas, Targanta Therapeutics

Wayne Thornton, Vertex Pharmaceuticals

Tiah Tomlin, Celgene Corporation

Bryan Topolewski, Hanford Pharmaceuticals

Okabe Toyotaka, Senju Pharmaceutical

Cua Trieu, Amgen

Krista Troilo, Vertex Pharmaceuticals

Jean Tronchet, Catelent Pharma Solutions

Philip Tsai, Seattle Genetics

Sina Um, MannKind Corporation

Gus Umpierrez, Pharmalucence

Natasa Uzelac, Immunogen

Robert Valdes, Human Genome Sciences

Miguel Valente, Bayer HealthCare Pharmaceuticals

Peter Valentinsson, Schering-Plough Research Institute

Bert Van Den Bosch, Optima Group Pharma

David VanderMeulen, BioMimetic Therapeutics

Sheri Varner-Munt, AMEC E&C Services

Adela Velazquez, Agencia Espanola De Medic Y Productos Sanitarios

Michal Voikovitz, Rafa Laboratories

Jinlu Wang, Sartorius Stedim Biotech

Christoph Wasem, CSL Behring

Dominique Weill, Sterigene

Tanya Weissman, Rafa Laboratories

Sarah Wilson, Alcon

Aretha Wilson, GlaxoSmithKline

Alexander Witz, BioMarin

Joerg Woerner, F. Hoffmann - La Roche

Justin Wright, Ultimate Labs

Yeo Saeng Yoon, M.D.GA

Zakaria Yusoff, Ben Venue Laboratories

Jochen Zenker, Vetter Pharma-Fertigung

Melanie Zipp, Sanofi Pasteur

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
Parenteral Drug Association
Connecting People, Science and Regulation®

2008 PDA Visual Inspection Forum

14-15 October 2008
Berlin, Germany

Conference, Exhibition 14-15 October
Training Courses 16-17 October

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

Register by 18 August 2008 and SAVE!

Visual Inspection continues to be an important element of the manufacturing process and the quality assurance of injectable products. This two-day interactive forum will closely examine: Latest Developments in Inspection Technology – Preparation and Use of Inspection Standards – Practical Aspects of Manual and Automated Methods – Regulatory and Compendial Requirements

Volunteer Spotlight

I'm proud to be a member of the PDA and glad that I picked up that first copy of the Journal all those years ago.

John Grazal

Senior Director, Global Quality–Operations, AstraZeneca

Education:

BS, Microbiology and Public Health, Michigan State University

MS, Systems Management, Florida Institute of Technology

PDA Join Date: 1987

Areas of PDA Volunteerism:

Various Task Forces

Events and workshops (presenter)

PDA Training & Research Institute (instructor)

Technical Report peer reviews

Professional Awards Won:

Certificates of Appreciation

Interesting Fact about Yourself:

I grew up in Detroit during the era when Motown and Chevrolet were preeminent.

Why did you join PDA and start to volunteer?

From the first time I read the PDA Journal, I knew that PDA was the organization that I wished to be a part of. I was immediately drawn to the caliber of articles it contained.

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

The series of workshops that PDA held globally on the 2004 revision of the FDA Aseptic Processing Guideline.

How has volunteering through PDA benefited you professionally?

The professional networking within PDA has been particularly invaluable. PDA provides so many opportunities to meet and collaborate with industry and FDA colleagues to accomplish work; [it] delivers a benefit to industry and ultimately to patients.

Which member benefit do you most look forward to?

The PDA Journal and the Technical Reports.

Which PDA event/training course is your favorite?

The PDA/FDA Meeting is always a highlight for me among the many outstanding events held by PDA.

What would you say to somebody considering PDA membership?

Do it! I absolutely guarantee that you will benefit from being a member of PDA. I have met so many talented people and have had so many opportunities to advance my professional capabilities as a direct result of being a PDA member and volunteer. I'm proud to be a member of the PDA and glad that I picked up that first copy of the Journal all those years ago.

Volunteer Spotlight

Stefano Macciò

President, PCTP Tecnologie Di Processo

Education: MA, Physics, University of Pisa

PDA Join Date: 1992

Areas of PDA Volunteerism:

PDA Italy Chapter

Professional Awards Won:

AFI (Italian Pharmaceutical Association) award as CTP Techologie Di Processo Co-founder

PDA Italy Chapter recognition for outstanding contributions in support of PDA activities.

Interesting Fact about Yourself:

When possible, I escape to the Elba Island. I have a nice house there with a beautiful view of the sea. I usually read, write and enjoy the landscape. I also like to hike.

Why did you join PDA and start to volunteer?

I joined because I thought that being a part of PDA would mean a lot for me and my company, since I could have access to a well-structured and high-level pharmaceutical network. A PDA member is constantly kept up to date with scientific innovations. PDA offers a wide range of professional resources that help members better understand new industry and regulatory developments.

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

Being one of the Co-founders and the current president of the PDA Italy Chapter

How has volunteering through PDA benefited you professionally?

I had many interesting business contacts and participated in high-level training courses.

Which member benefit do you most look forward to?

I really appreciate the fact that PDA offers a global network of industry and individual professional members, not to mention a wealth of educational and training resources.

Which PDA event/training course is your favorite?

My first PDA event that was held in 1999 in Italy about the validation and risk analysis in the manufacturing of sterile pharmaceuticals, bulk drugs and health care products.

What would you say to somebody considering PDA membership?

That PDA is the most foremost global provider of science, technology and regulatory information and education for the pharmaceutical and biopharmaceutical industry. PDA facilitates training and education on a global level and helps connecting people.

I really appreciate the fact that PDA offers a global network of industry and individual professional members, not to mention a wealth of educational and training resources.

Volunteer Spotlight

PDA provides a fast track for developing practical and scientific ways for sound implementation of upcoming regulations.

Stephan K. Rönninger

Global Quality Manager, F. Hoffmann-La Roche

Education: PhD, Engineering and Organic Chemistry, Technical University of Darmstadt

PDA Join Date: 2005

Areas of PDA Volunteerism:

Regulatory Affairs and Quality Committee (member and European representative)

PDA conferences and web seminars (speaker, committee member and/or moderator)

EMEA interested parties meeting (PDA representative)

PDA-PIC/S coordination (PDA representative)

PDA Letter (contributor)

Interesting Fact about Yourself:

Throughout my career I have always focused on visualizing and connecting interfaces. This also includes, for example, the development of a GMP based quality systems combined with safety/health/environment and business requirements. I have contributed to the development of ICH Q9; chaired the team for the Q9 briefing pack; and serving as an expert in the initial ICH Q8 based EFPIA sponsored mock P2 submission document.

I am really passionate about these tasks. If you ask my wife, children or friends they are probably tired of hearing my stories of traveling around the world for facilitating risk-based thinking. Personally, it is the most important contribution I have made to our industry and to the need of the Health Care Industry, which should be linked back to the protection of the patient who need the medicines we produce.

Why did you join PDA and start to volunteer?

In recent years, the regulatory requirements have changed dramatically supporting faster changes in technologies and environment. PDA provides an excellent platform to explore these developments and exchange ideas on technical, regulatory and GMP topics. PDA provides a fast track for developing practical and scientific ways for sound implementation of upcoming regulations. For me, PDA facilitates the interfaces among the pharmaceutical and biopharmaceutical industry, consultancies and regulators.

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

The scientific discussions and interaction with like-minded industry colleagues and regulators from all over the world. This has been a great opportunity. I appreciate the professional support of the PDA staff who are always helpful, open minded and responsive.

How has volunteering through PDA benefited you professionally?

I have benefited tremendously from the exchange of ideas and experiences with an international audience of people working in industry, consultancies and regulatory authorities. This has provided me with an excellent foundation for awareness, knowledge and all possible interpretation of current developments. My company strongly supports my PDA activities, which benefits all parties.

Which member benefit do you most look forward to?

From the publications, I like the new *International Pharmaceutical Quality* the most. Technical reports and articles in the *PDA Letter* are also a benefit by sharing good practice on science and technical issues without "raising the bar."

What would you say to somebody considering PDA membership?

I would tell them to take the opportunity to participate in a scientifically experienced environment. Make use of the wealth of knowledge and experience shared by PDA members to learn. For regulators, PDA participation could be valuable by providing pragmatic, straightforward support and discussion forums for current scientific, GMP and compliance issues.

Volunteer Spotlight

Susan Schniepp

Owner, Schniepp and Associates, LLC

Education: BS in Science, Northern Illinois University

PDA Join Date: 2000

Areas of PDA Volunteerism:

PDA/FDA Joint Regulatory Conference Steering Committee (member)

RAQC Committee (member)

PDA Letter (contributor)

PDA Training Class (instructor)

PDA Program Advisory Board (member)

PDA Membership Committee (member)

Professional Awards Won:

PDA Distinguished Author Award for *Understanding the United States Pharmacopeia and the National Formulary: Demystifying the Standards-Setting Process*

USP Award for contributions in leading USP industry stake-holders forum meetings

USP Award for contributions to the USP Reference Standards Program

Interesting Fact about Yourself:

I was elected to 2 terms on the Skokie, IL School District School Board, serving for 8 years.

Why did you join PDA and start to volunteer?

I joined PDA when I started working in the Hospital Products Division of Abbott Laboratories in 2000. The division made I.V. injectable products, and PDA was considered the premier organization for technical guidance and knowledge for parenteral products. I was asked to speak at the *2001 PDA/FDA Joint Regulatory Conference.* It was such an enlightening and wonderful experience for me because of the mentoring, coaching and encouragement from the PDA staff and members who were genuinely interested in my success.

PDA is a unique professional organization because it offers so much for its members. They have access to training courses, timely events and seminars, newsletters and technical information, and networking opportunities with other scientific professionals. The characteristic that sets PDA apart from other organizations is that they care about making sure members are engaged and getting value for their membership.

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

To me the most interesting, challenging and satisfying experience was being Chair of the *2007 PDA/FDA Joint Regulatory Conference*. I learned so much from my committee and the PDA staff about all the aspects to consider when developing a program and how to appeal to the audience to attend.

How has volunteering through PDA benefited you professionally?

Volunteering with PDA allowed me the opportunity to develop my organizational skills, hone my presentation skills and discover my writing skills. This allowed me to have the necessary skill set to start my own company. It doesn't get better than that.

Which member benefit do you most look forward to?

I really look forward to the *PDA Letter* and the *International Pharmaceutical Quality*. These publications allow me to keep current on what is happening in the industry on a global scale.

What would you say to somebody considering PDA membership?

Just do it! You will get so much from it—new experiences, new friends, new information, technical assistance, newsletters, etc. The value of the learning and information you have access to far exceeds the price of the membership.

Volunteering with PDA allowed me…to have the necessary skill set to start my own company. It doesn't get better than that.

Pharmaceutical Water Systems Discussed at PDA Israel Chapter Seminar

Ilana Zigelman, Zigelman Counsulting

On May 14, the PDA Israel Chapter held an enlightening and professionally delivered seminar to ninety participants on pharmaceutical water systems. Opening comments were delivered by **Mordechai Izhar**, PhD, and **Raphael Bar**, PhD, President of PDA Israel Chapter.

Avner Adin opened with a take-home presentation entitled "Drinking Water Regulations as a Source for Pharmaceutical Water." Avner's presentation included interesting concerns regarding the world's drinking water such as poisonous substances; pathogenic contaminants; causes of physiologic problems like magnesium and sulfate; and materials important to health like fluoride, calcium and potentially magnesium.

Avner pointed out that some poisonous substances are introduced naturally into our water supply and some are introduced by industry. He said that regulatory agencies around the world are slowly establishing limits for various organic materials. Avner chaired the drinking water standards committee which proposed use of Methyl Tertiary Butyl Ether as an indicator of ground water contamination by gasoline products. Water quality regulations are predominantly derived from public health, aesthetic and economic concerns.

Avner spoke about microbiological contamination and the use of indicator microorganisms because there currently are no methods to test for the broad spectrum of potential microbiological contamination of water. Particle size distribution is also used to indicate microbiological contamination.

The next speaker, **Shlomo Sackstein**, gave us a comprehensive review of two favored methods for chlorine removal, post reverse osmosis (RO) polish and reverse osmosis sanitation and distillation.

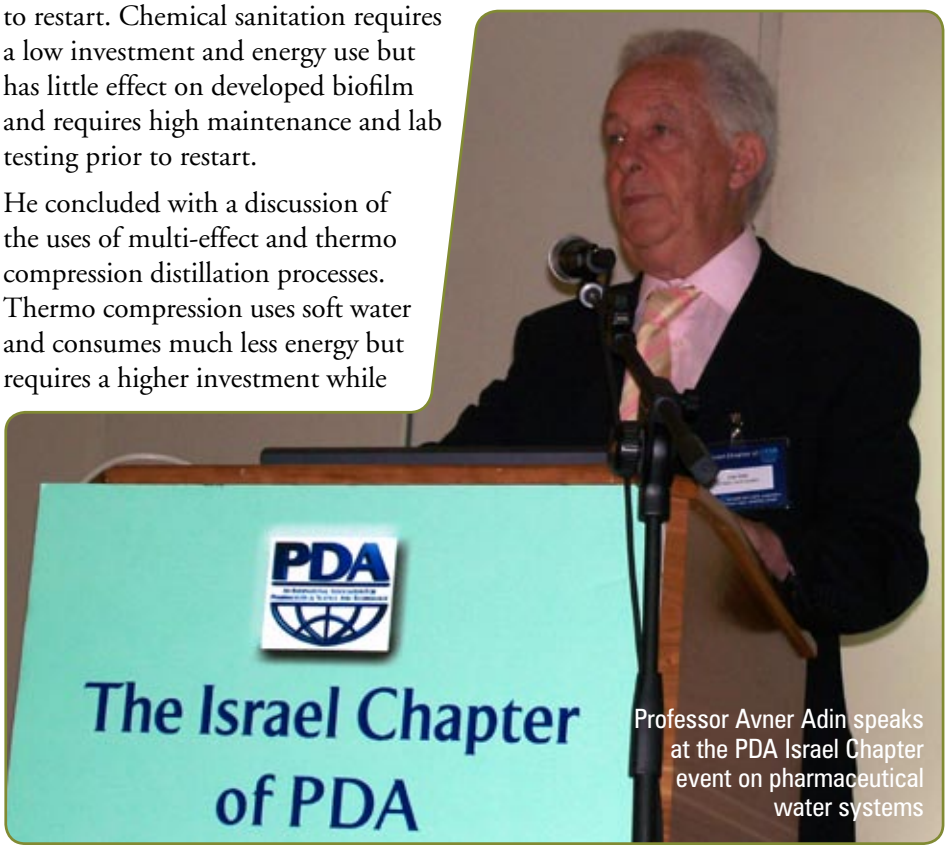
Shlomo started with chlorine removal options including use of either active carbon or sodium meta bisulfite (SMBS). Active Carbon is a simple and reliable procedure but is more expensive and may be problematic for controlling of biofilm. SMBS reduces the risk of microbiological contamination and is less expensive, but is not as reliable a procedure. Its tendency to overdose may lead to fouling of the RO membrane. Post RO polish options include use of a mixed bed resin or continuous deionization. Use of a continuous deionization requires no chemicals, moving parts or maintenance with consistent low conductivity and high quality but it is expensive to install. Mixed bed resin is less expensive to install and uses no power, however maintenance expenses are much higher due to required regular changes of the resin which increases the potential for contamination.

Shlomo went on to discuss the advantages and disadvantages of RO sanitation via chemical treatment or hot water sanitation. Hot water sanitation requires a high investment energy use but exterminates any developed biofilm with no need for chemicals or lab testing prior to restart. Chemical sanitation requires a low investment and energy use but has little effect on developed biofilm and requires high maintenance and lab testing prior to restart.

He concluded with a discussion of the uses of multi-effect and thermo compression distillation processes. Thermo compression uses soft water and consumes much less energy but requires a higher investment while multi-effect requires high quality feed water and demands a lower investment but consumes much more energy.

After the coffee break, we returned to an informative presentation by **Moshe Landsberg**. He started with insights into EU and US standards on various types of water, such as: USP/EP Purified Water (PW), EU Highly Purified Water (HPS)/USP Water for Injection (WFI) and EU Water for Injection.

Moshe concentrated on the fact that the differences between the three types of water are mainly in the production process, bioburden and endotoxin specifications and the various problems with water systems. Essentially problems with water systems derive from microbial contamination, rouge (from iron corrosion of the stainless steel) and silicates precipitation. Moshe reviewed basic control measures involved in pretreatment, final treatment and storage and distribution of different types of water systems like cold, hot, ambient and ozonated systems.



Professor Avner Adin speaks at the PDA Israel Chapter event on pharmaceutical water systems

Shlomo gave another presentation, this time on pharmaceutical water storage and distribution. He gave a comprehensive review of two of the more common standards for loop pipe surface finish, pipe loop calculations, loop sanitation options and for the different methods for loop cooling.

Surface finish options include electropolish or mechanical polish. Mechanical polish is more cost effective and is therefore more commonly available, but is less resistant to corrosion. Electropolish minimizes product adhesion (not relevant for water), removes the impurities on the metal surface and is highly resistant to corrosion but is more expensive. In hot systems, the benefits of electropolish are even further reduced due to annual passivation procedures which will remove the polish.

Shlomo next introduced the loop circulation options of minimum speed or turbulence. Minimum water speed in-loop is simple and easy to calculate and control, but requires a high investment in pipe diameter and high operating expenses. Turbulence in the loop requires a lower investment in pipe diameter, but validation is required for all pipe diameters and possibly supports biofilm growth by better transport of nutrients.

For sanitation/storage the use of ozone or hot water was presented with emphasis on the fact that there is really no justified reason for the lack of utilization of ozone sanitation. Ozone sanitation is fully automatic, requires little investment, is effective and does not use much energy while actively destroying Total Organic Carbon (TOC)/endotoxins, however the systems does require high maintenance and is a challenge to validate. Hot water is also fully automatic, will destroy any developed biofilm and requires no lab testing, however it is expensive and uses more energy.

Shlomo concluded by identifying loop cooling methods like heat exchange per point of use (POU) or central cooling. A POU heat exchanger can supply various temperatures of water if required but has many components, is expensive and is hard to validate. Central cooling is less expensive and easier to maintain but can supply only one temperature of water at a time.

After lunch **Rachel Karpel**, PhD, discussed pharmacopoeial requirements for water for pharmaceutical use. Rachel covered EP and USP requirements for production methods and specifications and appropriate uses. Water types include Purified Water, Water for Injection, and Water for Hemodialysis which are delivered in bulk. She also spoke about Sterile Purified Water, Sterile Water for Irrigation, Sterile Water for Injection, Sterile Water for Inhalation and Bacteriostatic Water for Injection, which are typically packaged.

Rachel pointed out that highly purified water is an EU water type that is not found in the USP and is intended for use in the preparation of medicinal products where water of high biological quality is needed. She also reviewed major concerns of range of separation for reverse osmosis, validation and maintenance of devices and microbiological aspects.

We were then introduced to validation of pharmaceutical water systems by **Kevin Greenstein**. Kevin started with a discussion of the regulatory basis for the requirements from USP and Pharm Europa. He then provided a glimpse into the complexity of water system validation from design documentation including Basis of Design, Piping and Instrumentation Drawing, Factory Acceptance Testing and ended with a discussion of basic validation IQ/OQ/PQ. Kevin's use of photographs and document samples was especially helpful as was his sharing of personal FDA inspection experience.

Ehud Halevi wrapped up the day with a comprehensive presentation about on-line monitoring in pharmaceutical water systems. He discussed on line options for control of TOC, Conductivity and Heat Sanitation. The required water quality will depend on the product for which it is used in conjunction with regulatory requirements. On-line monitoring provides the benefit of almost instant and accurate results and reduces the waiting time for laboratory results.

In all, this was an extremely informative and professional seminar on Pharmaceutical Water Systems. Many comments were given in appreciation of the professionalism of the speakers and of the relevance of their presented topics.

PDA's Who's Who?

Avner Adin, DSc Technology, Dipl.-Ing., P.E., Professor, Food & Environmental Sciences, Hebrew University of Jerusalem

Raphael Bar, PhD, Pharmaceutical Consultant, BR Consulting and PDA Israel Chapter President

Kevin Greenstein, Validation Manager, Colbar

Ehud Halevi, Technologist, Teva Oral Solid Dosage Jerusalem Plant

Mordechai Izhar, PhD, Validation Manager, Ludan Engineering

Rachel Karpel, PhD, Sr. Associate, PCI Pharmaceutical Consulting Israel

Moshe Landsberg, VP, Technology, BioCancell

Shlomo Sackstein, VP, Process and Validation, Biopharmax

PDA Puerto Rico Chapter, Amgen Hold Visual Inspection Conference

Manuel Melendez, Amgen Manufacturing

PDA's Puerto Rico Chapter and Amgen Manufacturing Limited (AML) joined efforts to celebrate an educational conference called, *Particles in Solution: a Visual Inspection Challenge* at the AML facilities in Juncos, Puerto Rico on May 22. The topic was of interest and pertinent to both pharmaceutical and biopharmaceutical industries.

The activity was attended by 36 representatives from the pharmaceutical and biopharmaceutical industries from: Wyeth, Bristol (BMS), Amgen and various local Consulting firms, including J. Alifonso & Associates; Jorge L. Tirado & Associates; Quality Improvement Trainers, Inc.; Asesoría Científica Ruiz & Cardona; and Artek, Inc.

Speakers at the event were **Raquel Dompenciel**, PhD, and **Miguel Carrion-Martinez**. Their joint presentation was about the challenges the company faced when transitioning from manual particles inspection process to an automated inspection process. The audience had the opportunity to ask questions about the topic and clarify important concepts related to the implementation of visual inspection and the challenges associated to the implementation of both manual and automated processes.

As moderator for the meeting, I discussed the importance of PDA's presence on the Island, considering that Puerto Rico represents 25% of the world's manufacturing capacity. This type of activity promotes the development of professionals in the pharmaceutical and biopharmaceutical industries in Puerto Rico, while keeping our members informed of the latest information regarding issues, regulations and advances in our industry.

The core team members of the Puerto Rico Chapter are composed of: **Evelyn Marchany, Miguel Montalvo, Gloria Martinez, Adalberto Ramirez, Thomas Kelleher,** PhD, **Iris Lucia Acosta** and **Frederick Fontanez.**

PDA's Who's Who?

Miguel Carrion-Martinez, Principal Engineer, Process Development, Amgen Manufacturing Limited

Raquel Dompenciel, PhD, Quality Engineering Director, Quality, Amgen Manufacturing Limited

Evelyn Marchany, Technical Services Director, Schering-Plough and PDA Puerto Rico Chapter President-Elect

Miguel Montalvo, President, Expert Validation Consulting and PDA Puerto Rico Chapter Member-at-Large

Gloria Martinez, Associate Director, Amgen Manufacturing Limited and PDA Puerto Rico Chapter Secretary

Adalberto Ramirez, Executive Director, QA, Amgen Manufacturing Limited and PDA Puerto Rico Chapter Member-at-Large

Thomas Kelleher, PhD, Director of Process Development, Amgen Manufacturing Limited and PDA Puerto Rico Chapter, Member-at-Large

Iris Lucia Acosta, Associate Director, Wyeth and PDA Puerto Rico Chapter Member-at-Large

Frederick Fontanez, Manager, QA, APP Pharmaceuticals Manufacturing and PDA Puerto Rico Chapter Treasurer

PDA
Parenteral Drug Association

The Universe of Pre-filled Syringes and Injection Devices

Regulators and industry experts will share case studies and address issues such as supplier qualification, materials of construction and considerations, filling and manufacturing, regulatory and compliance, safety systems and alternative injection devices.

Don't miss your chance to attend this one-of-a-kind meeting. This forum won't be back in the United States until 2010!

www.pda.org/prefilled2008

October 6 – 7, 2008
San Diego, California

Conference | Exhibition

PDA Australia Chapter Elects New Leaders, Holds Meeting

Robert Caunce, Hospira

Members of the PDA Australia Chapter recently elected new leaders in accordance to its charter. Succeeding **Anna Corke,** the title of President for the PDA Australia Chapter, has now been handed to **Robert Caunce. Ano Xidias,** has become the new President-Elect for the Chapter.

Having had the opportunity recently to attend the PDA Annual meeting in the United States, the Australia Chapter has a number of new ideas and initiatives to enhance benefits to local members.

PDA's Who's Who?

Robert Caunce, Compliance Manager, Hospira, and PDA Australia Chapter President

Anna Corke, QA Manager, Medical Developments International and PDA Australia Chapter Immediate Past President

Ano Xidias, Senior Consultant, PharmOut and PDA Australia Chapter President-Elect

The first industry meeting for the new group was held on the topic of filtration on May 13. The Chapter invited speakers from the three main filter suppliers which held the 120 industry attendees attention with information specifically from *PDA Technical Report No. 26, Sterilizing Filtration of Liquids* (which is undergoing revision) as well as from other PDA technical reports on filitration.

The industry night concluded with a panel discussion involving Q&A sessions with suppliers and two members Australia's Therapeutic Good Administration; it provided members an opportunity to ask a number of questions.

Normally having suppliers present at these industry meeting is an opportunity for a sales pitch about their products and companies—this time—it sounded like a sales pitch for PDA membership. As President, I took the opportunity to explain the benefits of being a PDA member, including the technical reports that were showcased at the meeting.

Continuing on the theme of PDA membership, the PDA Australia Chapter received some promotional material (i.e., pens and pins) that it presented to members in the audience as a sign of appreciation for continued membership.

In closing, the PDA Australia Chapter has a fantastic team. The initial meeting was entertaining and a credit to the committee and the speakers. The next event will be in July and more information will come out soon.

For more information about the PDA Australia Chapter, visit www.pda.org/australia.

ASQ, PDA Metro Chapter Hold Event

Nate Manco, ECO Animal Health

The PDA Metro Chapter and the American Society for Quality (ASQ) Princeton Section held their first and very successful joint dinner meeting on May 14 at the Ramada Inn in Somerset, NJ. **Eduardo Heidelberg,** and **Nate Manco**, were the masters of ceremonies for the evening. The meeting was attended by 117 people and included a display by vendor sponsor Sparta Systems.

Robert Seltzer, who led much of the effort to develop the new ASQ Certified Pharmaceutical GMP Professional program, gave a brief presentation on the purpose and value of the new certification. Workshops to develop exam questions and an ASQ Handbook are starting soon and the first CPGP pilot examination will be given in June 2009.

Nancy Rolli, was the featured speaker. Nancy spoke about the role of internal auditing in GMP management. In her presentation, she discussed the purpose of internal audits and items that should be included in the audit procedures and programs. She said that FDA normally will not ask to see internal or supplier audit reports, and relies instead on seeing the audit SOP, cover letter, schedules, etc. to see that a program is in place. This is to help company's assure that audit reports are sufficiently detailed and honest to be effective in getting correction actions and not "white-washed" reports.

PDA's Who's Who?

Eduardo Heidelberg, Chair, ASQ Princeton Section

Nate Manco, Director, ECO Animal Health Director, Immediate Past President of the PDA Metro Chapter

Nancy Rolli, Preapproval Inspection Manager, FDA NJ District, member of FDA's Foreign Inspection Cadre and also the Acting Director of Compliance Branch at the NJ District

New Chapter Leaders

Robert Johnson, Analytical Compliance Scientist, GlaxoSmithKline and PDA Metro Chapter Vice President

Robert Seltzer, Compliance Manager, Schering-Plough and PDA Metro Chapter Secretary

Lisa Smith, QC Analyst, Imclone Systems and PDA Metro Chapter Treasurer

Lara Soltis, Regional Sales Manager, ITW Texwipe and PDA Metro Chapter President

FDA will review and copy audit reports in "directed" or "for cause" inspections, in litigations or when executing a search warrant. These usually are situations where fraud, or serious injury or death has occurred, and FDA has a legitimate need to know who knew what and when.

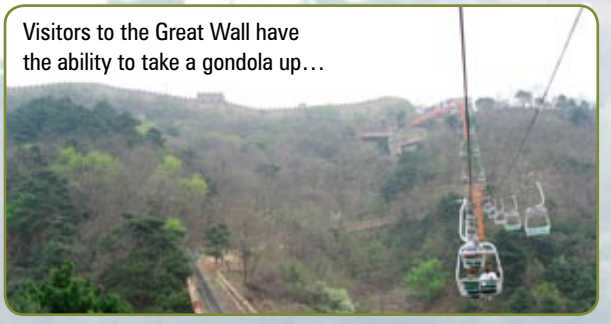
Nancy also indicated that FDA will always ask during an inspection for a list of "deviations," non-conformances, batch failures, out-of-specification (OOS) investigations and that experienced FDA Investigators expect to find that things happened—but it's how QA and company management react and deal with issues that is most important. She also presented the top 10 List of Drug GMP Citations in the NJ District—"QA not fully executing their responsibilities and written procedures" was the top item with "Production and Process Controls not being documented at time of performance" a close second. She also spent a lively 15 minutes answering questions from the audience and which was much appreciated.

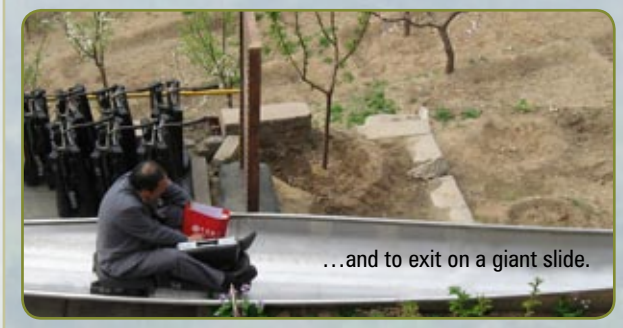
Nate and Eduardo presented Nancy with a plaque from PDA and ASQ in appreciation of her presentation. PDA Metro also held new officer elections that night. Congratulations to the new officers. For more information about the Chapter, visit www.pda.org/metro.

Faces and Places

PDA/FDA Co-Sponsored Conference Series on Quality Systems: Beijing and Shanghai

Visitors to the Great Wall have the ability to take a gondola up…





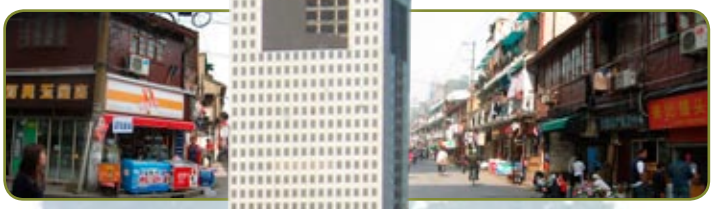
…and to exit on a giant slide.

Board members Steve Mendivil (far left) and Martin VanTrieste (with wife Cynthia) scout for Mongol invaders with PDA Staff

(l-r) John O'Sullivan, Pfizer; Martin VanTrieste, Amgen; Gerald Lohan, Merck

(l-r) Tim Marten, AstraZeneca; Neil Wilkinson, David Begg Associates; Barbara Allen, Eli Lilly; Fionnuala Walsh, Eli Lilly; Gregg Claycamp, FDA; John Gardner, FDA; Cliff Campbell, Campbell Informatics; Zena Kaufman, Abbott; Steve Mendivil, Amgen

Martin VanTrieste prepares to crack open "Beggar's Chicken"—chicken wrapped with two lotus leaves and covered with six pounds of pond mud.



(l-r) Zhou Qun, SHFDA; Yan Liang, SHFDA; Tang Minhao, SHFDA; Zena Kaufman, Abbott; Steve Mendivil, Amgen; Bob Myers, PDA

Risk Management and Aseptic Processing

Tara Gooen, FDA; Tom Genova, Global Biologics Supply Chain; Al Erario, Dey; Matej Janovjak, GPSG

(l-r) Martin VanTrieste, Amgen; Harold Baseman, ValSource; Kimberly Trautman, FDA

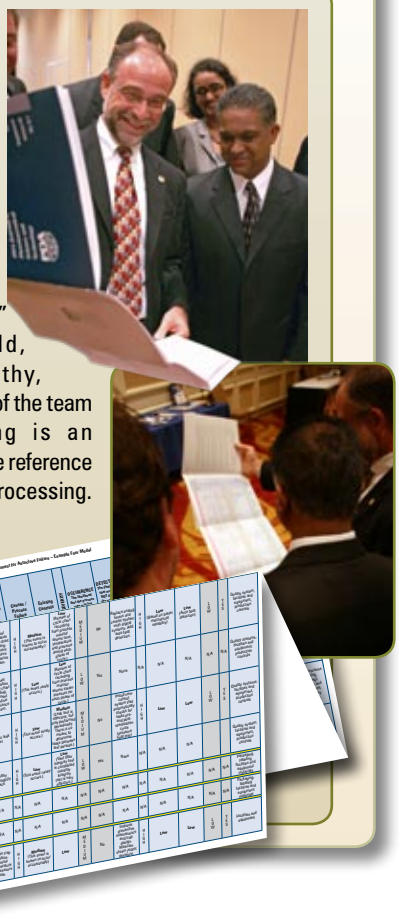
(l-r) Rick Friedman, FDA; Rich Levy, PDA; Martyn Becker, Martyn Becker Associates

(l-r) Jeff Hartman, Merck; Matej Janovjak, GPSG; Jim Akers, Akers, Kennedy & Associates; Joerg Zimmermann, Vetter Pharma; Jack Lysfjord, Lysfjord Counsulting; Al Erario, Dey; Martin VanTrieste, Amgen; Mike Long, AstraZeneca; Tom Genova, Global Biologics Supply Chain

The task force behind PDA's Technical Report 44 participated in the Risk Management for Aseptic Processing Conference.

The Task Force: (l-r) Marlene Raschiatore, Wyeth; William Miele, Pfizer; Kris Evans, Amgen; Harold Baseman, ValSource; Mike Long, AstraZeneca; Timothy Ramjit, Schering-Plough; Ruhi Ahmed, BioMarin Pharmaceutical; Jeff Hartman, Merck; William Harclerode, Forest Laboratories

TR-44 is PDA's first to have a tri-page fold-out. Perhaps surprising to some casual on-lookers, the "centerfold" that Harold, Ruhi, Timothy, and the rest of the team is admiring is an indispensable reference in aseptic processing.



Japanese Requirements on Agenda for 2008 Visual Inspection Forum

PDA Visual Inspection Forum, Berlin • October 14–17

Program Co-Chairs John Shabushnig, PhD, Pfizer and Markus Lankers, PhD, Rap-ID

Visual inspection continues to be an important element of the manufacturing process and the quality assurance of injectable products. Product inspection provides necessary information for lot release, and, coupled with defect identification, contributes to a strategy of continuous process improvement. Since 2000, PDA has organized the Visual Inspection Forum to discuss new technical and regulatory developments in this field.

This annual meeting alternates between the United States and Europe; this year's meeting will be held October 14–17 in Berlin. The meeting will provide a forum to present and discuss new developments in the field of visual inspection, including a basic understanding of the sampling and inspection process, practical aspects of manual and automated methods and the regulatory and compendial requirements that govern them. Special attention will be given to packaging component quality requirements and inspection requirements and practices for the Japanese market.

This is an excellent opportunity to learn more about visual inspection and to discuss inspection challenges with the experts. We have provided time in the program for networking with the speakers and for discussion of your specific inspection challenges. As in past years, the meeting will feature an exhibition where attendees can see the latest in commercial inspection hardware and discuss production needs with key suppliers of inspection systems and services. A special vendor session in the program will provide the opportunity for a brief overview on their latest developments.

We are also pleased to add again an optional two-day training course offered through PDA's Training and Research Institute. This course covers the basics of the inspection process and its application to injectable products. It will be a combination of lecture/discussion and hands-on laboratory exercises used to develop and practice practical inspection skills. The skills developed through this course may be applied to both manual human inspection and automated machine inspection. This course will be held immediately following the Visual Inspection Forum on October 16–17 in the same location.

For more information on the Visual Inspection Forum and related TRI course, visit www.pda.org.

We look forward to seeing you at this exciting and informative meeting!

Broad Range of Topics and Speakers Highlight the 2008 PDA/FDA Conference

Washington, D.C. • September 8–12 • www.pda.org/pdafda2008

Bob Dana, PDA

Have you registered yet to attend the 2008 PDA/FDA Conference: *Harmonization, Implementation, and Modernization: Achieving a Future Vision*? If not, time is running out, so make your plans today. This year's conference has more of a global focus than in previous years—an important note as businesses have become more global in nature.

Wednesday, September 10th, the last day of the conference has some truly exciting and important sessions you won't want to miss. The morning starts with your choice of five different breakfast sessions; learn while you have your coffee or tea!

One session will be devoted to considering some of the scientific challenges associated with conducting bioequivalence studies; **Lawrence Yu,** PhD, a pharmacologist in FDA's Center for Drug Evaluation and Research (CDER) will speak at this session. At a second session, Boehringer Ingelheim's **Norbert Hentschel** is scheduled to discuss the work of the team revising PDA Technical Report No. 14, *Industry Perspective on the Validation of Column Based Separation Processes for the Purification of Proteins*. If you're interested in the chromatographic separation and purification of proteins, this is the breakfast for you.

Japanese regulatory authorities have issued their Aseptic Processing guidance document, and this will be discussed in a unique interactive format with attendees at this breakfast session. Just be careful not to eat your cereal and talk at the same time!

Two other sessions will explore how FDA has incorporated risk assessment in their business operations. Accomplishments and lessons learned from their Risk Based Inspection Approach will be discussed by **Gregg Claycamp,** PhD, CDER's Associate Director for Risk Analysis and Strategic Policy Assessment. Abbott's **Zena Kaufman**, Divisional Vice President, Quality Center of Excellence, will also participate in this breakfast roundtable. This is sure to be a dynamic and popular session.

Seating at the breakfasts is limited and on a first come, first serve basis, so be sure to register early. Information about registering for breakfast sessions can be found in the program brochure or at www.pda.org.

Once the breakfasts are over, the meat of Wednesday's sessions gets under way. The first of two plenary sessions will cover FDA compliance issues. **Kim Trautman,** Consumer Safety Officer, FDA's Center for Devices and Radiological Health, and **Martine Hartogensis,** DVM, Deputy Director of the Office of Surveillance and Compliance in FDA's Center for Veterinary Medicine, have confirmed their participation in this session, as have **Mary Malarkey,** Director at CBER's Office of Compliance and Biologics Quality and **Joe Famulare,** Deputy Director, CDER's Office of Compliance. Confirmation from a representative of the Office of Regulatory Affairs is in process at this time. The value to attendees at this session is that they will hear directly from senior compliance staff about how the concepts associated with quality systems have changed the way FDA does business, as well as learning what the regulatory impact has been to industry with regard to implementing quality systems. In addition, FDA representatives will describe their efforts to develop and implement internal quality systems and will provide insights into how their own Quality System Guidance and ICH Q10 has impacted those efforts. As appropriate, FDA staff may also provide an update on the status of the proposed changes to the drug product GMPs which were announced in December 2007. Those who attended the GMP Compliance session at last year's PDA/FDA Conference will remember how well attended and informative that session was, and this years promises to be just as enlightening.

The conference will conclude with a second plenary session which will include presentations by the Center Directors or their representatives on updates and highlights of ongoing and planned future initiatives in the Centers for Biologics, Devices, Drugs and Veterinary Medicine, as well as the Office of Regulatory Affairs. CBER's Senior Advisor for CMC Issues, **Chris Joneckis,** PhD, will address these topics for CBER and Hartogensis will make a return to describe programs planned and underway in CVM.

Deb Autor, Director, Office of Compliance, CDER and representatives from both the Office of Regulatory Affairs and the Center for Devices have also been invited, and are expected to take part. You certainly won't want to miss hearing from these senior FDA representatives on their efforts to move the global harmonization process forward.

Lest you think that all the action only takes place on Wednesday, be assured there is plenty to hold your interest on Monday and Tuesday as well. Speakers from global regulatory agencies, including China and Europe, as well as FDA and USP will address

Network at the *2008 PDA/FDA Joint Regulatory Conference*

Kathleen Greene, Novartis Pharmaceuticals; Eric Sheinin, PhD, Sheinin & Associates; and Susan J. Schniepp, Schniepp & Associates

PDA believes it is important for attendees of its conferences to have time to interact with each other as well as with the conference presenters—participants benefit from personal contacts. Networking simplifies and encourages the discussion of current issues, exchange of mutual concerns, sharing of experiences and finding solutions benefiting the participant and the pharmaceutical community.

The *2008 PDA/FDA Joint Regulatory Conference* will continue to "connect people, science and regulations" by offering attendees multiple opportunities to interact with opinion leaders from industry and regulatory agencies. FDA representatives will participate in nearly every session at the 2008 conference offering the Agency's current thinking on various topics affecting the industry. Participants can network directly with opinion leaders via several venues:

- During the Q&A period of each concurrent session
- During morning and afternoon refreshment breaks
- At PDA Interest Group meetings
- During the networking reception and Gala evening events
- In the exhibit area
- Throughout the conference and between sessions (most speakers attend the conference)

These networking venues and the interest group meetings offer participants numerous and varied ways to make connections with individuals experiencing similar situations in their careers and companies.

In addition to networking with people on a business level, PDA networking activities also offer attendees the option to connect with others on a personal and more social level. Many attendees of these meetings have developed lifelong friendships.

Plan to attend the *2008 PDA/FDA Joint Regulatory Conference*, September 8–12, and take advantage of the opportunity to meet new colleagues; you never know when you will have need of the expertise of one or more of your new contacts.

harmonization issues on Monday in the opening plenary session. On Tuesday, another plenary session will discuss the perils and pitfalls in moving from an SOP based approach to quality and compliance to the adoption and implementation of a comprehensive quality system approach. Numerous concurrent sessions over the first two days will address a broad range of compliance and quality issues; and a number of PDA's popular Interest Groups will be meeting on Monday and Tuesday. There will be two sessions combining the efforts of multiple Interest Groups. On Monday, the Lyophilization and Parenteral Drug Manufacturing Interest Groups will be meeting in a joint session, and on Tuesday, the Biotech and Vaccines Interest Groups will combine for a joint meeting. Other Interest Groups meeting during the conference include:

- The new Prefilled Syringes and Quality Risk Management Interest Groups
- Facilities and Engineering
- Combination Products
- Clinical Trial Materials
- Pharmaceutical Water Systems
- Visual Inspection of Parenterals
- Filtration
- Process Validation
- Quality Systems

The hard part will be deciding which sessions to attend!

As the saying goes, "all work and no play make a dull boy," so the Program Committee has allocated some time for social activities as well. The always popular PDA Gala will be held Tuesday night at the National Music Center. As in the past, this event promises to be a fun filled evening with food, music and dancing, and provides a great opportunity to renew old friendships and make new ones.

Speaking of new friendships, there will be a special breakfast on Monday morning for new PDA members, so if you've joined PDA since April 1, 2008, this is the spot for you to learn more about PDA and the benefits of your membership. There will be a luncheon on Tuesday where you can learn more about how to volunteer and the opportunities of being a PDA volunteer.

To get the most from your travel dollar, take advantage of the opportunity to remain in Washington, D.C., and participate in one of the training courses being offered by the PDA Training and Research Institute on Thursday and Friday, following the Conference.

If I may close on a personal note, I've been attending the PDA/FDA Conference since its inception. I've always found it to be an incredibly interesting and informative Conference in the past; and I know this year's Conference will continue in that tradition. I encourage you to join me and your colleagues at this year's PDA/FDA Conference. Go to www.pda.org/pdafda2008 on a regular basis and check out the meeting updates.

I look forward to seeing you in Washington, DC, September 8–12.

PDA TRI Offers Best in Faculty, Facility and Flexibility

James Wamsley, PDA

TRI TALK

It's that time of year again for TRI as we begin scheduling and budgeting for the upcoming year. As I sat here trying to figure out a reasonable schedule, I wondered if there was some easier way to plan well over a year in advance. I don't know what I'm having for lunch tomorrow, but I can tell you what courses we're offering 17 months from now!

I'm sure many of you are in similar situations in deciding where to spend what little training money is available and justifying where to spend it. While I'm positive you have set aside funds for your own training or that of your staff for 2009, maybe you are still debating on where to send your employees for that training. Making a commitment to send someone for training to an organization like PDA is a big investment for a company and an endorsement of your company's belief in that employee's ability and potential. There are probably several questions floating through your head, all of which center around how to choose the best training for your employees. Well, I'm going to help you through that difficult decision making process.

There are several reasons to choose PDA TRI over our competitors. Faculty, facility, staff and flexibility are just four of those reasons. Each of these factors contributes to the success that TRI has enjoyed over the past several years. They are also the same factors that make TRI such a great place to receive training.

The first and most important reason for the success of TRI is our faculty. Our faculty is among the best and brightest experts in the pharmaceutical industry. They are dedicated, intelligent and very generous individuals who have spent countless hours passing on their knowledge to course attendees. Their motivation is neither financial nor ego-driven—it is focused on the patient and improving the quality of the products being used by those patients in the healthcare system. Our faculty members are consultants, industry personnel and regulators whose common thread is their expertise in what they teach. They don't stretch themselves too thin by trying to teach too many different topics; instead, they focus on what they know best. This is the reason we have almost 20 faculty members for our *Aseptic Processing Training Program*. Each faculty member teaches a specific topic during the two-week course. This approach benefits our students by allowing them to interact closely with someone who has intimate knowledge of the subject being taught

While it is easy to say that the TRI facility is such a great asset because it closely mimics a pharmaceutical or biopharmaceutical environment, that is not the only reason it is successful. The biggest reason is that the facility is built for training and only training. The facility is dedicated 100% of the time to running laboratory or lecture training courses, and it is always ready and stocked to run a course. It is also the only facility of its type not related to an academic institution that provides the kinds of hands-on laboratory training for which PDA is known. The year-old facility in Bethesda is more efficient than our old site, enabling us to run more courses with more people. Although we have created more opportunities for our members to attend training at our facility, we still strive to achieve an ideal student to faculty ratio of 12 to 1—a goal we set as part of our commitment to quality over quantity.

Another contributing factor to TRI's success, and not a small one I might add, is the staff. While some of our competitors make training just a small part of their business, our staff is fully committed to training. Whether we are running a lecture or laboratory course, on-site or off-site, stand-alone or in conjunction with a large meeting, our focus is always on successfully running the training courses. By devoting all of our time to training, we continue to improve the quality and execution of our courses. Because we are not distracted by tasks unrelated to our programs, we are able to keep in touch with and abreast of the current hot topics within the industry, and continually help develop and seek out training that is most important and relevant for our members and non-members alike.

Certainly the reasons detailed above should justify making TRI your choice for training. Another important consideration is TRI's flexibility. You may be unaware that TRI will tailor courses specifically to your needs. For example, we can run our lecture or lab-based courses at our facility in Bethesda or at your facility, and the topics can specifically address your company's training needs. All you need to do is call or write and we will work with you to develop the perfect training course. If you have a large group in need of the same training, then why not save some money and have us come to you?

While I've only detailed four key factors to the "why go to TRI" question, there are many other contributing factors that have made TRI successful. Hopefully, I've helped you make your decision, but if you still need more information regarding our courses and capabilities, please feel free to contact us at any time. You can find our contact information, as well as pictures of the facility, directions, video, and a course calendar, on our redesigned website at www.pdatraining.org. And if you are in the neighborhood, please visit us and take a personal tour of PDA TRI!

TRI Demonstrated Its Capabilities at the 2008 PDA Annual Meeting

A Complete Educational Experience in Downtown Washington, D.C.!

Washington, D.C. • September 11–12 • www.pdatraining.org/pdafda

Tim Morris, PDA

PDA TRI has always been dedicated to developing a comprehensive curriculum to help those in the industry to improve their professional development. This curriculum takes place both in and out of the laboratory, with training courses offered in the classroom around the country and around the world. In many cases, these valuable courses are held along with some of PDA's most exciting signature conferences…and the *2008 PDA/FDA Joint Regulatory Conference* will be no different!

Following the PDA/FDA Conference, TRI will host its *2008 PDA Regulatory Conference Courses*—eight classroom courses that will cover issues relevant to quality assurance/control, regulatory affairs, GMP auditing and manufacturing, as well as several others and complement the topics being presented at the Conference. In fact, 2008 gives students a chance to attend their choice of three new additions to the TRI curriculum:

1. "Combination Products: Principles, Regulations, Current Issues and Solutions" offers students a discussion, review and interpretation on relevant laws, regulations and guidance for drugs, biologics, medical devices and combination products
2. "Effective Application of a Quality Systems Approach to Pharmaceutical cGMPs in Compliance with the FDA Guidance" reviews the FDA guidance on quality systems. The course defines the concepts behind the establishment of quality systems to drug operations and the specific elements discussed within the guidance.
3. "Establishing and Operating an Effective GMP Audit Program" details the perils and pitfalls in establishing and running an effective GMP audit program.

These new courses are lead by **Michael Gross,** PhD, RAC, Chimera Consulting; **Miguel Montalvo,** Expert Validation Consulting, Inc.; and **Bob Dana,** PDA. Each gives participants unique insight to the complexities of the industry in hopes of translating their tutelage to a sincere professional growth opportunity for students.

Other courses offered this year at the Renaissance Hotel include: "Biopharmaceutical QA/QC for Senior Management"; "Global Regulations and Standards: Influences on Cold Chain Distribution, Packaging Testing and Transport Systems"; "Preparing for and Managing FDA Inspections"; "Change Control: A Practical Workshop"; and "Improving Sterile Drug Submissions to the FDA."

If you are making a trip to Washington, DC for the *2008 PDA/FDA Joint Regulatory Conference*, let TRI complete your journey with one or more of these eight lecture courses! And while you're in DC, come visit our TRI facility in Bethesda, which has reached its one year anniversary.

PDA Training and Research Institute
EDUCATION • TRAINING • APPLIED RESEARCH

SEPTEMBER 11-12 | WASHINGTON, D.C.
www.pdatraining.org/pdafda

Educational Opportunities Await you in Washington, DC

The PDA Training and Research Institute will be conducting several lecture courses following the *2008 PDA/FDA Joint Regulatory Conference*. This year's offerings include:

SEPTEMBER 11

- Biopharmaceutical QA/QC for Senior Management
- Combination Products: Principles, Regulations, Current Issues and Solutions NEW COURSE!
- Risk Management in Aseptic Processing NEW COURSE!

SEPTEMBER 11-12

- Effective Application of a Quality Systems Approach to Pharmaceutical cGMPs in Compliance with the FDA Guidance NEW COURSE!
- Global Regulations and Standards: Influences on Cold Chain Distribution, Packaging Testing and Transport Systems
- Preparing for and Managing FDA Inspections

SEPTEMBER 12

- Establishing and Operating an Effective GMP Audit Program NEW COURSE!
- Change Control: A Practical Workshop
- Improving Sterile Drug Submissions to the FDA

Contact:
Stephanie Ko
Manager, Lecture Education
+1 (301) 656-5900 ext. 151
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Location:
Renaissance Hotel
999 9th Street, NW
Washington, DC 20001

PDA Parenteral Drug Association *Connecting People, Science and Regulation®*

ISPE

PIC/S PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

A Workshop for Industry and Regulators Presented by PDA & ISPE with PIC/S

Manufacture of Sterile Medicinal Products EU/PICS revised GMP Annex 1

New and Possible Uses of Quality Risk Management

A Unique Opportunity: Presented by PDA & ISPE with the Pharmaceutical Inspection Cooperation Scheme, this workshop is designed for industry practitioners and inspectorates. It will provide an opportunity to discuss and learn about the uses of QRM in the design, operation, and quality auditing of aseptic manufacturing processes for medicinal products. The workshop will allow inspectors and industry scientists to share discussions and problem solving using QRM approaches to address major issues in aseptic processing.

Purpose of Workshop: (1) Provide training and experience to regulators and industry professionals in the GMP application of Quality Risk Management principles in manufacture of sterile medicinal products, (2) Provide opportunity for collaborative technical discussions between industry and regulators, fostering communications and concrete problem solving.

Workshop Format: Following introductory presentations the workshop attendees will break into smaller, facilitated groups made up of industry and inspector representatives. Each group will address four technical topics of common concern in aseptic processing. The discussions will involve the application of QRM thinking to these topics, with a learning opportunity for all participants to share viewpoints and technical knowledge. The outcomes will be summarized as learning materials for future application.

Technical Topics: The workshop is conducted in the context of PIC/S - EU GMP Guide including Annex 1 for Sterile Medicinal Products. Each group will discuss best approach, including QRM, to take on case studies associated with four key topics:

1. Capping
2. Media fills (process simulation)
3. Continuous monitoring, clean area classification and ISO Norms
4. Sterilisation and depyrogenisation of contact parts and containers

13-14 November 2008
Hotel Moevenpick
Geneva, Switzerland

Workshop/Exhibition: 13-14 November

For more information & to register:
www.pda.org/europe

Register by 13 Oct 2008 and SAVE!

To Be or QbD!

Frankfurt, Germany • October 7–8

Mohammed Barak, Batrox and Volker Eck, PhD, PDA

This or something similar could be our motto for the PDA Conference and Exhibition on Quality by Design (QbD) on October 7–8 in Frankfurt-Offenbach. We are privileged to have with us distinguished speakers coming from very different sectors of the pharmaceutical compartment. You will meet **Kowid Ho** from the French Health Authority (AFSSAPS) as well as **Mats Welin** from the Swedish Agency (MPA). Also speakers from big and small pharmaceutical companies presenting their efforts and results obtained when embarking into Quality by Design concepts; not to forget suppliers, who have collaborated in order to create was needed.

To give you an idea of what you will hear and see, we want to share with you three examples of what will be presented.

Beppe Mazzochi, PhD**,** Merck, Italy, will try to convince you that developing and scaling up a new product with QbD and PAT concepts is an exciting and cutting edge science experience which requires a strong commitment and sponsorship.

The presentation will initially focus on Merck's experience starting from some prerequisites; it will provide an overview of the choices that need to be performed before starting the process and then during routine manufacturing operations. Also, the advantages experienced in Merck will be presented. The impact on people and the integration with the existing Quality Systems will be described and practical examples will be provided.

In the second part of the presentation the NIR assay method used for Real Time Release will be discussed. An overview of the process to design, optimize and validate the prediction model will be discussed. The presentation will include a reference to partial least square method and to metrics used to optimize the model as well as an explanation of what a model rank is and its impact on prediction results. Finally outlier diagnostics meaning, importance and their practical use will be examined.

Paul Dickinson, PhD, AstraZeneca, will elaborate on QbD, and good pharmaceutical quality which has been defined in 2004 by **Janet Woodcock**, MD, FDA, as "an acceptably low risk of failing to achieve the desired clinical attributes." This challenges biopharmaceutical scientists, as pharmaceutical manufacturing will need to link product clinical performance to manufacturing attributes (Critical Process Parameters–CPPs/ Critical Quality Attributes–CQAs). Traditional methods for measuring clinical quality (i.e., clinical pharmacokinetics studies) are not viable when the large number of batches generated during process establishment are considered, as it is not feasible to test all batches in the clinic. New methods are therefore required. *In vitro* dissolution testing is a key tool for this purpose and the present bioequivalence guidelines and biopharmaceutical classification system (BCS) provides a platform for regulatory applications of *in vitro* dissolution as a surrogate for safety and efficacy. However, to support QbD, the application of dissolution needs to be further developed by exploiting the higher level of understanding presented in regulatory documentation and risk based concepts that are also an important element in the new regulatory paradigm (ICH Q9).

This presentation will discuss and exemplify how clinical quality can be assured via dissolution testing in the context of QbD with emphasis on BCS class II drugs.

Stéphanie Passot, PhD, AgroParisTech/INRA, France, will lecture about QbD in lyophilization technology. As you might know, lyophilization or freeze-drying is widely used to preserve proteins and polypeptides, which are physically and/or chemically unstable in aqueous solutions. The process involves freezing of the aqueous protein solution, followed by primary drying to remove ice by sublimation, and, secondary drying to remove unfrozen or sorbed water.

The application of an quality by design approach in the field of freeze-drying process faces numerous obstacles. One of the most important ones is that product conditioning in single-use vials just before starting the process makes it impossible to implement some PAT tools: and subsequently the use of multivariate statistical analysis for describing the state/quality of the product.

Developing a rational approach to identify the relevant formulation attributes and the critical process variables for manufacturing stable freeze-dried products is the real challenge of today. This presentation will elaborate on an efficient application of an experimental design for freeze-drying needs, illustrate a previous approach based on the identification of the stress mechanisms involved during freeze-drying and the stabilization mechanisms allowing preserving biological activity of the active ingredient.

The following points will be discussed:

- Why any experimental design approach must be used with caution?
- What the best methodology is for formulation screening and to optimize the freeze-drying cycle?
- How statistics tools could be used in the future to improve process understanding and optimization?

We hope that these short abstracts have peaked your interest, and that we see you at the conference!

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2008 PDA/FDA Joint Regulatory Conference

Harmonization, Implementation and Modernization: Achieving a Future Vision

September 8-12, 2008
Washington, D.C.

Conference	September 8-10
Exhibition	September 8-9
Courses	September 11-12

www.pda.org/pdafda2008

The US Food and Drug Administration (FDA) announced the Good Manufacturing Practices (GMPs) for the 21st Century initiative in 2002, giving the industry its first glimpse of the future of regulatory oversight for pharmaceutical production. The intent of the original initiative was to offer the industry the necessary tools to provide more post-approval flexibility, making continual improvement less of a regulatory burden, and to promote better self-regulation to improve regulatory compliance status.

In the five years that have passed since the announcement, regulatory health authorities and industry have partnered by harmonizing requirements and implementing new systems for assuring and maintaining pharmaceutical quality. The 2008 PDA/FDA Joint Regulatory Conference will provide examples of how these new approaches have been successfully implemented. In addition, the conference will examine what is working well and where the industry and regulatory health authorities still need to work to achieve modernized quality systems.

PDA is also offering an exhibition during the conference. The PDA Training and Research Institute (PDA TRI) will host courses immediately following the conference to complement what you learn at the meeting.