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PDA Letter

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In This Issue:

PDA℠
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Urgent Action Required for Supply Chain Security: Report from the PDA/FDA Conference on Supply Chain

Michael Awe, APP Pharmaceuticals

[Editor's Note: This is a summary of the proceedings of the conference attended by the author and contains portions of materials presented at various sessions. For a full conference report, please visit www.pda.org to download the web seminar of the conference proceedings.**]**

Presenters at the *PDA/U.S. FDA Pharmaceutical Ingredient Supply Chain Conference,* December 3–5 in San Diego, Calif., issued a collective call for urgent action to ensure the integrity of drug products. More than 120 professional representing 30 companies were in attendance.

The conference, a follow-up to one held in September in Washington, D.C., focused on addressing the recent rise in contamination and/or misidentification of ingredients that entered pharmaceutical and other consumer products around the world. Well-publicized incidents included melamine found in baby formula and pet foods, diethylene glycol found in glycerin used to make cough syrup, and over–sulfated chondroitin sulfate found in heparin.

The meeting organizers, presenters and FDA officials who attended the 2½ day conference reviewed the incidents described above, presented strategies and techniques for addressing the problem, and issued a call for urgent action to the attendees.

The proceedings included a summary of the *FDA Globalization Act*, which is a piece of legislation drafted by the Committee on Energy and Commerce of the U.S. House of Representatives, requiring a number of new measures intended to improve the safety of the supply chain. These measures include annual registration of all domestic and foreign firms supplying drugs or devices into the United States; "prompt" FDA inspections of these once they are registered; country of origin labeling for API's; an electronic statement or "pedigree" identifying each prior sale; purchase and trade of the API or excipient; and the requirement for companies to create quality risk management plans that along with assessing and controlling risk will determine the supplier's "suitability and competence" to supply API's or excipients.

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Pharma firms are finding that third party audits are one of many ways to secure the supply chain. Photo collage by James Austin Spangle.

Coming Next Issue:
U.S. FDA's New Revised Validation Guidance

Editor's Message

Change of Leadership and Changing Times

In January, as we were preparing the February issue of the *PDA Letter* for the presses, our workflow was interrupted by the millions of visitors to the Washington, D.C. area who were here to celebrate the inauguration of the new U.S. President. The PDA headquarters is only eight miles to the U.S. Capitol building, where the oath of office took place. Local governments closed for the day, including schools, forcing some of us to take the day off. Other PDA staff decided to spend the day in D.C. to witness the historical event. Indeed it is a time of change, not only in D.C. and in America, but in our industry globally as well.

The top challenge facing the new U.S. President is similar to the top challenge of the pharmaceutical industry—how to manage resources in these tough economic times. Unfortunately, tough times force tough decisions; jobs will be shed, product lines reduced, salaries will be frozen or cut. PDA is not immune to these tough decisions. So over the last year, we've been closely evaluating our publishing activities to align them with the new economic realities. As such, the *International Pharmaceutical Quality*, *PDA Journal of Pharmaceutical Science and Technology* and the PDA Technical Reports will only be available to members as electronic publications moving forward. This tough decision ensures that PDA will continue to disseminate high quality knowledge that helps our community of members do their jobs better.

Despite the tough times, the work of our industry must continue. So as some struggle with the challenging decisions and others suffer from them, still the vast majority of us must ensure that the important life-saving medicines we produce continue to be made. In this issue of the Letter, we offer once again an examination of the supply chain issues that became the front and center concern of the industry and the regulators last year. It is even more important in this belt-tightening atmosphere that firms spend the time and resources necessary to guard against contaminated, adulterated and counterfeited supplies.

We wish our members well as we all deal with the current economic malady.

Correction: The *PDA Letter* erroneously published that new PDA Director Junko Sasaki works for the U.S. FDA, when in fact, she works for Sumitomo Pharmaceuticals where she is responsible for submissions to the U.S. FDA. We apologize to Junko, Dainippon Sumitomo Pharmaceuticals and the U.S. FDA for the mistake.

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PDA To Host Process Validation Workshop, Sterilization Conference

PRESIDENT'S MESSAGE

Bob Myers

I am pleased to announce that PDA will be hosting two new meetings starting next month in San Juan, Puerto Rico. These events are the *Sterilization Technology Today and Tomorrow* conference and the *PDA Workshop: The Shifting Paradigm in Process Validation*.

The ***Sterilization Technology Today and Tomorrow*** conference will examine recently improved methods and technologies—as well as those in production for future use—for the sterilization of materials, components and finished bio/pharmaceutical products. These new standards have been developed by PDA in conjunction with U.S. FDA and EU regulators, and represent the most advanced approaches to sterilization. You will hear directly from the experts who wrote these sterilization guidance documents.

At the ***PDA Workshop: The Shifting Paradigm in Process Validation,*** FDA representatives who were actively involved in the preparation of the *Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach* will discuss the draft guidance and what to expect when investigators come to your plant for an inspection. This is also your chance to influence and provide input for this new FDA initiative.

PDA will host the conference and workshop again in various locations around the world throughout 2009:

Sterilization Technology Today and Tomorrow

San Juan, Puerto Rico
February 18–19

San Francisco, California
March 2–3

East Brunswick, New Jersey
May 14–15

PDA Workshop: The Shifting Paradigm in Process Validation

San Juan, Puerto Rico
February 20

San Francisco, California
March 4

Munich, Germany
March 9

Las Vegas, Nevada
April 23

Chicago, Illinois
June 8–9

Bethesda, Maryland
October 26–27

I hope to see you and your colleagues for these events in 2009.

Bob Dana Assumes TRI Responsibilities

In January 2009, **Bob Dana,** a long time PDA member and industry leader, assumed responsibility for Education and TRI as Sr. VP of TRI and Regulatory Affairs. Dana will continue to report to **Rich Levy,** PhD, Sr. VP, Scientific and Regulatory Affairs, PDA and serve as PDA's regulatory authority.

Bob is well-known by PDA members and regulatory experts at the U.S. FDA and EMEA. He also has previously been an instructor and leader at TRI.

Myers said that he expects TRI to continue to be a flagship operation, and build on its unique first class Bethesda manufacturing and laboratory facility that enhances PDA's hands-on-training.

In 2009, Myers predicts that TRI will have record attendance in its *Aseptic Processing Training Program*. To date, the training program is sold out for the first part of the year.

According to Myers, TRI is also in the process of conducting training for new biotechnology reviewers in FDA's division of Manufacturing & Product Quality within CDER.

PDA's Training and Research Institute offers initial training to members in quality control just joining the pharmaceutical industry.

Bob Dana

Science & Technology Snapshot

PDA Journal and Technical Reports Go Electronic in 2009

Rich Levy, PhD, PDA

PDA has embarked on an ambitious plan to create a new, online scientific experience that will not only enhance the *PDA Journal of Pharmaceutical Science and Technology,* it will forever change the way you read and use the Journal and the Technical Reports.

We have partnered with Stanford University's HighWire Press, a leader and innovator in providing online scientific resources for over 13 years. The HighWire portal now hosts over 1,180 websites, including journals, reference works, books and other resources. We encourage readers to check out some of their offerings at the following websites to get a full understanding of what to expect from PDA's new online Journal:

Proceedings of the National Academy of Sciences
www.pnas.org

Cleveland Clinical Journal of Medicine
www.ccjm.org

Disease Models & Mechanisms
dmm.biologists.org

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It is our intent that the new website for the Journal will offer many of the features that you see at the above referenced HighWire websites.

It is our intent that the new website for the Journal will offer many of the features that you see at the above referenced HighWire websites. We hope all our members and readers can see the value these high quality websites will bring to the Journal.

The new journal website is targeted to launch sometime in the summer of 2009. It was PDA's intention to continue printing and mailing the Journal until the new website launches. Unfortunately, with the tough and uncertain economic times, we feel it is not possible to continue expending the resources to print and mail each issue at the same time we are bearing the cost of building the new website. So, starting with the next issue (vol. 63, no. 1), PDA will be offering the Journal as a PDF file at www.pda.org/journal. Members will be required to logon to the website to access the PDF. We anticipate that only two Journals will be posted in this fashion before the new website launches. This decision also impacts PDA's technical reports, which will be published at the new website.

We thank you for your understanding and patience during this time of transition.

Technology *Trend*

Campaigning with RABS

Emily Hough and Walter Morris, PDA

Use of Restricted Access Barrier Systems (RABS) in aseptic processing is becoming more popular in the industry as an alternative to isolators, although companies employing RABS must take particular care to ensure they meet regulatory expectations. Use of isolators and RABS is allowing companies to extend their traditional fill run times. [**Editor's Note**: For a more detailed discussion of RABS, see "RABS Risks and Rewards—A Discussion with FDA's Rick Friedman and Brenda Uratani," in the July/August 2008 *PDA Letter*, p. 30.]

At *PDA's 3rd Annual Global Conference on Pharmaceutical Microbiology,* GlaxoSmithKline discussed how the use of RABS for the sterile antibiotic cephalosporin has allowed the company to implement a filling "campaign." Presenting the case study was **Marco Malaguti,** PhD, Chemist, Quality Director, for GSK's Verona facility.

According to Malaguti, a filling campaign is the length of time that a setup may be maintained on the filling machine before it requires disassembly and resterilization. Generally, companies filling in campaign mode are processing many more lots per setup, increasing capabilities and saving money. Many companies have joined GlaxoSmithKline in developing filling campaigns.

Malaguti noted that there are few standards and guidelines for setting up campaigns, except with respect to validation. The U.S. FDA recommends that *factors associated with the longest permitted run on the processing line that can pose contamination risk are addressed during media fill programs.* A PIC/S guide recommends that *where filling takes place over extended periods, i.e., longer than 24 hours, the process simulation test should extend over the whole of the standard filling period.* Both the FDA and the EMEA (in Annex 1) require the establishment and validation of time limits for aseptic fills. Neither agency, however, explicitly defines maximum campaign length or describes validation requirements, limitations or other restrictions.

The expectation, Malaguti said, is that "each activity or operation that could compromise the sterility of the product should be avoided or minimized and, in this case, its impact must be evaluated."

GSK's Approach

Malaguti provided details on the cephalosporin filling campaign that GSK has established. He highlighted the unique factors the firm addressed in establishing a multiday fill campaign for the sterile dry powder product.

To highlight the factors that had to be addressed to set up this sterile dry powder filling process, Malaguti compared the process with the more traditional sterile liquid fill. A

continued on next page

Journal *Preview*

Vol. 63, No. 1 – A Who's Who of PDA Scientists

Walter Morris, PDA

The Journal starts 2009 with two compelling "Commentary" articles by well-known PDA scientists: **Ted Meltzer** and **Russ Madsen** were part of a group commenting on the new EMEA position on reverse osmosis as a means of WFI production; **James Agalloco, James Akers** and **Russ Madsen** joined a group to analyze the convergence of risk management, cGMPs and aseptic processing technology. The "Research" articles in the issue include an analysis of airborne particles by the well-known PDA contributors, **Bengt Ljungqvist** and **Berit Reinmüller.**

Commentary

- T. Meltzer, R. C. Livingston, R. E. Madsen, M. W. Jornitz, R. M. Johnson, M. W. Mittelman, "Reverse Osmosis as a Means of Water For Injection Production: A Response to the Position of the European Medicines Agency"
- J. Agalloco, James Akers, Hal Baseman, Richard Boeh, Russell Madsen, Steven Ostrove, and Anthony Pavell, "Risk Management, cGMP, and the Evolution of Aseptic Processing Technology"

Research

- Umit Kartoglu, Serge Ganivet, Stephane Guichard, Venkat Aiyer, Peter Bollen, Denis Maire, and Birhan Altay, "Use of Cool Water Packs To Prevent Freezing During Vaccine Transportation at the Country Level"
- Sonia Driss Chaieb, Jean-Claude Chaumeil, Sami Jebnoun, Naima Khrouf, Abderrazek Hedhili, Souad Sfar, "Effect of High Calcium and Phosphate Concentrations on the Physicochemical Properties of Two Lipid Emulsions Used as Total Parenteral Nutrition for Neonates"
- E. García-Montoya, M. Queralt, P. Pérez-Lozano, J. M. Suñé-Negre, M. Miñarro, J. R. Ticó, "Total Organic Carbon (VCSN AND VWP) And HPLC Analysis For Cleaning Validation In A Pharmaceutical Pilot Plant"
- Vishal Gupta, Meenal Gupta, Anil Kumar Madan, "Development of Modified Dosage Form for Enhancement of Dissolution Rate through Amalgamation of Solid Dispersion and Cube Sugar or Sintering Technology Using Famotidine as a Model Drug
- Stefan Sundstrom, Bengt Ljungqvist, Berit Reinmüller, "Some Observations on Airborne Particles in the Critical Areas of a Blow-Fill-Seal Machine"
- N. Ranjha, "Polymeric Micelles of Ammonium Palmitoyl Glycol Chitosan and Solubilization of Camptothecin"

Technology Trend: Campaigning with RABS, continued from previous page

big difference involves equipment cleaning and sterilization. For sterile liquids, CIP/SIP is a consolidated practice and expected at most facilities. "This is unthinkable for powder," Malaguti said. "CIP/SIP is not applicable for the form of the product, and [equipment] parts are aseptically assembled by operators."

Other differences include setup times and batch sizes. "Setup is longer than for liquid," he said. "For liquid, long holding times can produce product sticking; in the powder the product can remain in the machine without sticking." Batch sizes have no limitations for the powder, he added, whereas storage tank size limits the batch for liquids.

The firm had a choice between a "continuous" campaign or a "multiday" campaign, and chose the latter. Malaguti said a continuous filling campaign would entail a "single long run" with no stoppages for maintenance. He described the multiday campaign as a long run with some "fine tuning every day."

Campaigning is an attractive alternative to lot-by-lot filling, because it reduces the risks inherent to the process setup. "In powder aseptic filling, equipment setup is the most critical aseptic operation because it requires human interventions and because of that it is difficult to standardize—we have to rely on the people," said Malaguti. The setup "is the longest intervention, and it can take one hour to beef up the machine—much more than what is required to just move a vial that has fallen down during the operation." A poor setup can result in several interventions during production.

GSK Verona set up a run that involves the receipt of the API ready-to-fill, and no blending required at the filling site. The aforementioned RABS technology is used on four manufacturing lines, and the validated maximum campaign is five days, which would involve ten total personnel shifts (two-per-day).

This multiday approach reduces the number of setups, thus reducing the related risk of contamination.

Validation

Malaguti outlined a number of points from the media fills used to validate the multiday campaign. The general attitude is that "contamination of any unit being filled by aseptic processing occurs as a result of an event rather than as a function of time." Therefore, the duration of the media fill was established to the time required to fill the requisite number of units and to simulate all of the identified interventions.

The media fill simulates "as much as possible" the routine process. All contamination risk factors are considered and represented. First the company fills for the entire duration of the campaign, which is for five days. During this media fill, 10,000 vials are filled using both PEG (to simulate the product) and TSB. Then the company conducts two trials covering the full duration day, encompassing about 6,000 vials.

Increase Quality, Reduce Costs

Malaguti noted that firms need to customize their fill campaign "based on process and production scheme, products to be aseptically filled and environment and technology used."

Campaigning offers a number of advantages, he said. Companies can minimize the time their machines are down and can maximize the time to produce drugs. Campaigning is applicable to single or multiproduct facilities. "You can have bigger batches or multibatch campaigns, or we can have a changeover for multiproduct with the machine, if it doesn't require to change the API."

Malaguti summed up his presentation by reiterating the idea that while there are few specific regulatory requirements for filling campaigns, there are definitions of appropriate time limits and validation through media fills. He also stressed that while a campaign is an opportunity, it needs to be well designed.

PDA Interest Groups & Leaders

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

SECTION TITLE

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

SECTION LEADER

Frank S. Kohn, PhD *FSK Associates*	David Hussong, PhD *U.S. FDA*	Don E. Elinski *Lachman Consultants*	Sandeep Nema, PhD *Pfizer Inc.*	Robert L. Dana *PDA*

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Recent Sci-Tech Discussions: "Design Space" Designations

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.

Friends—two questions:

A. Am I correct that, since Ajaz Hussein, PhD, left the U.S. (about 2 years back), the concept of "Design Space" has dropped out of the "hot topic" list on the conference and lecture circuit?

B. Am I correct that in the current economic climate, if any companies were involved with Design Space, they have since curtailed or eliminated research in this area?

Respondent 1: [Questioner], Design space may or may not have dropped out of the hot topics circuit, but it has been codified in ICH Q8, making it likely that you will be asked about it by your local regulatory body. I can say that there certainly using the design space concept for various processes such as lyophilization.

Questioner: [Respondent 1], Thanks, but please tell me why "top FDA" folks still occasionally talk about it at conferences, but local FDA inspectors seem to be either clueless or indifferent to the QbD concepts?

With Best Regards.

Respondent 2: Dear [Questioner], [Respondent 1] is correct in that companies are implementing the QbD and design space concepts during development. However, the general acceptance has been slow both by the industry and by some regulators. I do believe that—with further education on the utility of QbD—its adoption will become more prevalent earlier in development. Now, I am just speaking from a formulations-fill-finish perspective. However, QbD is already currently very common in the industry, and regulators are used to seeing such data in cell culture-fermentation. That's my take based on recent conferences and represents my personal opinion.

Respondent 3: [Questioner], Quality by Design (concepts of design space/knowledge space/control space) is being exploited by many companies working with biologics, particularly the bigger ones.

Theory says that there are significant cost savings to be had by adopting a QbD approach over the life cycle of a product. However, you are quite correct that people are unaware, or indifferent, to it. The problem is that the concept is somewhat complicated and most people don't get to understand or just see it as metaphysical. In fact, in many ways, it has been around for years, we just did it in another way.

Unfortunately many examples of the application of QbD are over-complicated, and what's really needed are simple clear explanations of its application (anybody out there got one?).

Judging by the meeting reports I've read, European regulators are certainly working on its application too, and PDA has held several conferences on the subject. They also just published in the *Journal of Pharmaceutical Science and Technology* (September-October 2008) a report on a workshop on QbD for Biopharmaceuticals for those interested.

Respondent 4: [Respondent 3], You mention that we just used to do it in another way. So is QbD what I used to call parametrization? We always used to develop products by looking at the variable, same for chemicals. Having established a preferred pathway, we would look at such things as solvents, temperature and time, etc.

Having done that we would select an operating range. For example, for a reaction, it might be 80°C for 4 hours, but we would know that we could do the reaction at 75° or 85° without affecting quality. Would that be what is now considered design space, in other words, an increase in flexibility based on experimental results?

If this is so, why do we have to invent new terminology?

Respondent 5: [Respondent 4], I agree with your conclusion. Having come from the chemical industry, where I held positions of Research Chemist, Manufacturing Process Supervisor, Research Manager, Technical Director and Vice President of Research and Development, what is intended by "design space" and "QbD" was standard practice for sound product and process research and development. Extensive knowledge surrounding product and process was always developed, well beyond what was required to bring a process to plant.

Regards.

Respondent 6: Design space is old wine in a new bottle in many aspects. The "Proven Acceptable Range" concept has been around many years and was being addressed in process validations. Design space is a fancy word that attracts attention right away. I tip my hat to whomever coined design space.

Respondent 7: Dear [Respondent 4], All roads lead to Rome. QbD, design space, and parametrization lead to robustness.

Best Regards.

Respondent 8: Dear [Questioner], I am afraid your observations are not correct this time. Design space as part of a Quality by Design (QbD) marketing authorization is alive, and many bigger and smaller classical pharma and biotech companies worldwide are spending significant money on QbD. Some

examples from the recent (October 7 & 8, 2008) PDA conference on QbD in Germany:

- Marketing authorization for a medicinal product using QbD and applying a design space to support real time release of the product.
- A medical device process went out of control. Applying the principles of QbD (risk assessment, design of experiments, statistical analysis and design space development), the process was brought back to its specifications, and yields were significantly improved over the original process.
- Real time control of a lyophilization process using a design space based upon in-line temperature measurement.

The examples above are not R&D dreams, they are reality and are applied today. As a conclusion of this meeting, the concept of QbD is not only alive in talking; many companies apply QbD as a whole, or certain parts of it, and by doing so already benefit from QbD.

Meetings like the PDA conference on QbD this year in Germany attract significant numbers of people (over 100 participants), and see basically three groups of attendees: one group whom is listening and silently working on QbD projects at their company (often because some departments do not want to change current procedures or because senior management does not see the benefits of applying QbD). The other group are companies successfully applying QbD processes (some with product that have marketing authorization, but the majority with products that are in the pipeline) and reporting the gains of QbD both technically and financially. The last group of attendees are the regulatory authorities. These people have cleared the road to apply for a marketing authorization using QbD principles in their own organizations.

So to the end, QbD and all its subcomponents, like risk assessment, design of experiment, multivariate analysis, Process Analytical Technology (PAT), design space and continuous validation, are more and more applied in the biopharmaceutical industry, and more companies see the benefits. To me QbD is very much alive.

If you wait a while, the next issue of the *PDA Letter* will give you the full overview of the PDA QbD meeting last October. **[Editor's Note:** The article in reference was published in the January issue, p. 46.**]**

I trust this gives you a better overview of where QbD stays today.

Kind regards.

Respondent 1: [Respondent 4], If you include the interaction between variables, then you have what I understand is design space. In your example, you would demonstrate that your reaction can operate at a 75–85°C for 3–5 hours.

I don't see ICH Q8 and QbD as a radical departure from what has been done before, other than the increased reporting requirements.

It is indeed an increase in flexibility based on experimental results. As far as the new terminology, it seems that in this industry, there is a tendency to reinvent the wheel, or at least to rename it.

Respondent 1: [Respondent 5], I agree with you and [Respondent 4]. One of the things I have seen from the validation end of things is that sometimes the extensive knowledge developed during process research and development is not adequately transferred beyond the R&D department. I don't see ICH Q8 and QbD as a radical departure from what has been done before, other than the increased reporting requirements.

Respondent 3: [Respondent 4], It looks like the design space posting is generating some interesting comments.

Yes, in fact, my particular remark that you cited which was directed at biopharmaceuticals was in reference to a parametric analysis of process parameters, enabling a good understanding of the process in question. And yes, that approach has seen much application in the past. Probably most classical microbial fermentation product processes were optimized that way.

Nevertheless, I don't believe it's just new terminology. As a philosophical basis of approach, I would argue that QbD goes much further than just a parametric analysis and seeks to create a comprehensive understanding of product and process. In order to illustrate that point and for those readers not familiar with the concept, see attached some data from the PDA Journal article I mentioned in my previous posting. It shows the classical (current) and QbD approaches.

Hope that illustrates the points or maybe provokes some more debates....

Regards.

Respondent 6: Hi [Respondent 3], Comprehensive understanding of product and process has been the focus of the industry for a long time before QbD came into existence, and the main reason being economic advantage. QbD has given a new slogan and new attention because of all the hoopla and what not. As it is well known, clever marketing is important as developing a unique product to meet unmet medical needs.

Respondent 3: Judging by the varied responses to the question on design space (more appropriately, Quality by Design, QbD) people either love it or hate it and think that it's a reincarnation or a marketing extension or even something that they've been doing for years.

Some of it has been done before, so maybe some of the above can be justified, perhaps maybe not; maybe its just that people don't understand, or want to [disparage] a subject for which they see no value.

One thing is certain (and without reiterating the contents of the mail of [Respondent 8] is that QbD has been taken on board by regulatory authorities and by many biopharmaceutical companies as a means of developing products and manufacturing products more effectively. These points are facts.

The beauty of this forum is that it permits all points of view to be expressed and aired, and I imagine that the general aim should be to help people better understand topical issues or resolve a problem. Sometimes this illustrates progressive opinions which move with the times or those who prefer to stay with the past.

Regards.

Respondent 7: Dear [Respondent 3], It is not as simple as that (love or hate). What I would like to say is that a new terminology coupled with a road map is worth looking at.

Regards.

Respondent 9: Dear [Respondent 1], Welcome to the world of pharmaceuticals, where the science of nature has almost completely been forgotten. Reinvent the wheel? Goodness me no...they will redo the wheel four hundred thousand times over [at different companies at a huge cost] using the same model from 1918. Forget about "going forward" with the newer model that came out in 1919. This is all about "looping."

It is sad because, every month, trillions of dollars are wasted in validating things we already know about nature when this cash should actually be spent upon R&D...but this is silly...how can one spend in research when, after all, the validation of the product process will ruin the corporation? This does not include the current fad of applying GMP to laboratories? GMP is to creation as is a vacuum is to normal atmospheric pressure! Guess what? Nothing comes out of the labs suddenly! I wonder why that is?

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Baxter's Strategy for an Increa

Emily Hough, PDA

At the *2008 PDA/FDA Pharmaceutical Ingredient Supply Chain Conference* **Matthew Anderson** shared supply chain improvements which Baxter has been employing over the last few years. He said that implementing a new strategy helped Baxter deal with an increasingly unpredictable and intricate global supply chain.

Anderson, Corporate Director, Global Supplier Quality, Baxter, told audience members in December 2008 in San Diego, Calif., that it was important to have a plan that detailed what the company would be doing to improve the drug supply chain. "It's very important that you share that plan with senior management and you share it with your internal stakeholders to make sure you have agreement and alignment." He also said that is was important to routinely review the plan to "show ongoing alignment and support."

Enhancement

In addition to making more long-term goals, one of Baxter's immediate plans was to review high-risk suppliers. (This plan included verifying historical performance; looking at its supplier's suppliers; reviewing test methods and looking for areas of improvement and ensuring that the firm has transparency in the drug supply chain.) Baxter then turned its attention to programs already in place. In terms of its auditing program, for example, Anderson said that Baxter increased the length and frequency of audits, standardized the auditing training program and gave auditors additional training. Audit reports were also expanded to include new requirements. For example, Baxter now requires that if an audit is held in a foreign country where English is not the first language, an independent native language translator will participate in the audit if a Baxter employee that speaks the language is not present.

Detection of contamination, enhancement of tamper evident technologies and progression of Baxter's new supplier approval program are other areas that have been rethought. Anderson said that "we started to think like the bad guys, and we started to think in terms of 'what if,' and we began to take actions to reduce the risks of what historically we would have considered 'improbable' or even 'unimaginable.'"

Another area that was further improved was Baxter's emergency action plans. Baxter employees are now role playing and running drills in artificially created environments to prepare for whatever potentially comes across their desk.

Anderson emphasized the importance of thinking of suppliers as an extension of an organization. He said that it is very important to have transparency with suppliers. "You need to understand who they are and what their capabilities are and because again they are an extension of you." Baxter is implementing a supplier-based rationalization project, whereby it will look at significantly reducing its supplier base and the number of suppliers that it interacts with to reduce the complexity in its supply chains, and therefore focus its additional energy on those suppliers it retains. Anderson said that Baxter is "significantly retooling our supplier risk model to correlate with our new thinking. This includes things like suppliers from emerging markets will now be looked at as a higher risk and while Baxter always sought out desired partnerships with our suppliers, today we are taking proactive steps to foster and encourage those types of relationships."

Innovation

Baxter created a number of cross-functional task forces to deal with issues like tampering and brand integrity. The firm is also taking a careful look at how non-pharma companies manage supply chain issues.

Figures 1–5 are slides Matthew Anderson presented outlining Baxter's Supply Chain Strategy

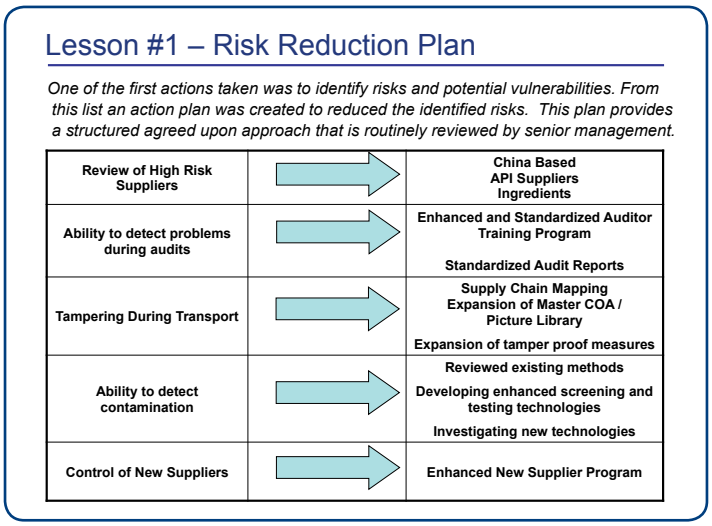

Figure 1

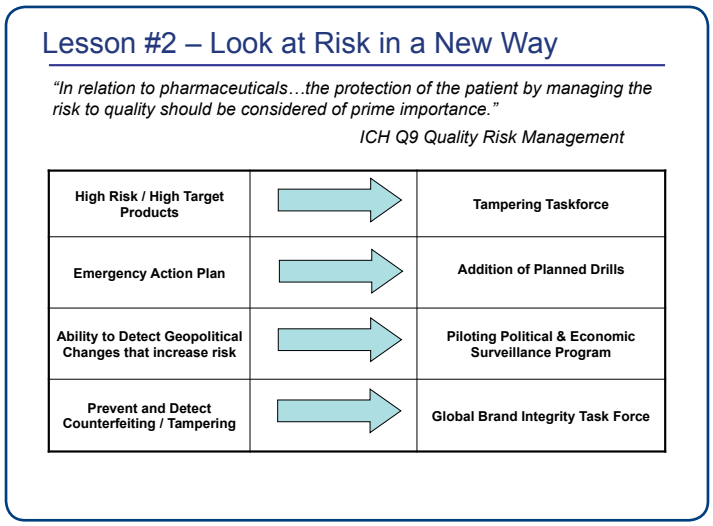

Figure 2

singly Globalized Supply Chain

Baxter's task force on tampering is such a "solution." This cross functional team looked (and continues to look) at the entire Baxter catalogue which includes over 1,000 lifesaving medicines. The team looks for high-risk high-target products, for example, high-risk products that are used in critical care situations or critically ill patients. Baxter looks for indicators such as a high number of units being sold, and the uniqueness of the product that would make it desirable as a target for fraud contamination. "We are using a risk-based approach to try to identify those that we believe are the highest risk of the highest target products and making sure that those get priority review to make sure that we have the right robust quality security systems around."

Baxter has also created a task force to address global brand integrity. This is another cross-functional team that is led by Baxter's global security group with dedicated resources whose whole emphasis and focus is on identifying, preventing and detecting opportunities for counterfeiting and tampering.

Among other remedies, Baxter has created a political and economic surveillance program to make it easier to detect shifts in both political and economic situations which may drive suppliers to cut corners or take risks that impact product safety. For instance, the firm will monitor new risk factors like changing commodity prices or supplies, and then evaluating how the market forces impact its supplier's behavior.

Baxter is also reaching out to other industries like the automotive and electric industry to try and benchmark and learn from their historical experiences. Baxter is then figuring out how to incorporate the successes of other industries into their more modern supplier quality program. "I would encourage all of us to think outside of the industry—look for historical lessons and examples as we look for solutions to these problems as we shape the future."

Anderson closed his presentation with the following advice: "A final lesson is that [a solution] is going to require an integrated effort. Internally, you have to have your management on board, you have to have your internal stakeholders and you need to pull in other parts of the business. This is too big for the quality organization to do alone.…I believe that if we continue to work together to set new controls and standards, identify risk and solve those risks in new and innovative ways we have a tremendous opportunity to reduce potential risk that occurs in supply chain and potentially to our customers."

Lesson #3 – Supplier Base Knowledge

Suppliers are an extension of your organization. Ultimately the manufacturer is responsible for the quality and safety of their medicines.

Large Complex Supplier Base	→	Supplier Base Rationalization
Supplier Risk Model	→	Emerging Markets Continuity of Supply Performance Metrics with well defined remediation / elevation Supplier's "Suppliers" Strategy Enhancing Reduced Testing Programs
Supplier Partnerships	→	Scorecards Sharing of Knowledge Just-in-Time Delivery Communication Enhanced Quality Agreements

Figure 3

Lesson #4 – Look Outside the Industry

Often the problem faced has been solved or partially solved, but you may need to look across industries for it to be identified.

Detection Technologies	→	Airport Security
Traceability of Supply	→	Shipping Companies
Supplier Management	→	Automotive / Electronics Historical Teaching (Deming / Juran)
Centralized Notification	→	Crime Stoppers Hotline
Knowledge Sharing	→	Internet Information Sites Internet Social Network Sites
Seller's Performance	→	eBay

Figure 4

Lesson #5 – Integrated Effort

To achieve our vision of a safe supply chain, it requires a integrated effort within each company, suppliers, industry, regulatory bodies, and the customer.

Within Baxter	→	Senior Management Support & Internal Stakeholders Use of Third Parties / Consultants
Suppliers	→	Industry Groups Desire for Cooperation / Partnerships
Industry	→	Supplier Quality Discussion Group Industry Groups Consortium Standard Setting Organizations
Regulatory Bodies	→	Partner with Industry Mutual Recognition Guidance / Legislation
Customers / Patients	→	Voice of Customer

Figure 5

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Urgent Action Required for Supply Chain Security: Report from the PDA/ FDA Conference on Supply Chain, continued from cover

One suggestion mentioned repeatedly by representatives from both industry and the International Pharmaceutical Excipients Council (IPEC) was the use of third party audits to help both individual companies cover their many suppliers and to provide a general database that, for a fee, other companies could access for their own use. The goal is to *maximize* audit resources of pharma companies and to *reduce the burden on excipient manufacturers of similar multiple audits*.

It is noteworthy that conference participants emphasized that *third party audits are acceptable to the FDA,* and none of the FDA representatives present refuted this statement.

While the meeting addressed many issues, it is important to make note of three main ones that relate to the reasons pharmaceutical companies must actively work *now* to secure their supply chain:

1. Rapid globalization leading to supply chains becoming potentially very far flung and complicated due to cost pressures, the use of brokers and intermediaries and the acquisition of more and more ingredients from API and excipient suppliers in emerging markets (such as China) are becoming more common.
2. The state of suppliers in these emerging markets when compared to the United States, Canada, Europe and Japan have adopted GMP's only—relatively recently, (i.e., within the last 20 years).
3. The movement of "criminals" into the pharmaceutical supply chain, who see it as a source of a "quick buck."

Referencing the above contamination incidents, the resulting sicknesses and, in some cases, the tragic loss of life, representatives from the FDA, leading companies and the IPEC urged attendees to help create a "consortium" that would meet in early 2009 to discuss harmonized standards and a strategy for quickly putting preventative measures in place now. This suggestion of a consortium is strongly supported by suppliers at the meeting, such as Sigma-Aldrich, who view it as a relief to the burden of doing audit after audit.

However, presenters made a good point that companies should *do something now* and not wait for a consortium, a perfect plan or a standard to be established. Some key suggestions provided by the 22 presenters fall under the following nine categories:

1. Suppliers and Supply Chain

- Create a scorecard that rates suppliers in terms of quality (including audits and sample analysis), delivery and service (considering too, post-purchase services).
- Perform a periodic review of a supplier's performance. Review the trend in non-conformances and CAPA efficiency.
- Implement a photo system in which the API/excipient specification contains a *picture* of what the container and label should look like. If a different container or label arrives, immediately suspect the material's acceptability.
- Check your brokers. Use of brokers can lead to lack of traceability of the API. A solution is to check the "step-by-step" shipping, repacking and other processes that brings the ingredient to your dock. The more links, the more chances for diversion, contamination, etc. Be particularly cautious when the API is repackaged; broker's containers might not offer ➤

Words To Live By: Notable Quotes from the Conference

"The Future is Now!!"

— Rick Friedman, Director, Division of Manufacturing and Product Quality, CDER, FDA

"Move suppliers up, or *out*" (i.e., help you suppliers improve their processes. If they can't improve or won't, replace them with another supplier).

— Martin Van Trieste, Vice President, Quality, Amgen

"You need a strong relationship and 'face time' with your suppliers."

— Paul Vogel, Senior Corporate Advisor, Lachman Consultant Services

"Stop the Whining!" (In response to those who offer excuses to not look harder at their supply chain because of costs, resources, etc.)

— Martin Van Trieste, Amgen

"Think like a Criminal!"

— Numerous presenters

"Complying with regulations should be considered a *minimum* requirement" and "Be proactive!"

— Deborah Autor, Director, Office of Compliance, CDER, FDA

"Let's Roll!!" (Quoting the "call to action" of Todd Beamer on United flight 93 on 9/11/2001)

— Edwin Rivera-Martinez, Chief, Manufacturing Assessment and Pre-approval Compliance Branch, Office of Compliance, CDER, FDA

"There needs to be greater international cooperation among regulatory authorities."

— Bronwyn Phillips, Pharmaceutical Inspector, MHRA

"I think you are going to see legislation on these proposals ...and I think that is going to drive the question: What exactly should be the purpose of pedigree, what should it look like, and how expansive?...I think that is going to be a reality that people are going to have to address." (Responding to an audience question about pedigrees)

— Jennifer Devine, Acting Division Director, Division of New Drugs and Labeling Requirements, CDER, FDA

the same protection. (Stability is a concern.)

- Look for critical points in the chain. When found, make the supplier add more controls. Examples were provided of brokers revising Certificates of Analysis (COA) to suit their needs. The pharmaceutical company must certify the integrity of the COA's. Insist on a name and address of the original manufacturer in the COA (not a subsequent repackage/broker/etc.), signed by the QA representative..
- Develop a strong partnership with suppliers. Do not let the quality relationship simply consist of the original audit, followed by the periodic "follow up" audits. Trends performance, change control and continuous improvement should be taken into account.

2. Risk Analysis

- Pfizer, Amgen and Baxter all presented their strategies for Risk Assessment, following the philosophies outlined in ICH Q8, Q9, and Q10. This type of analysis is *crucial* in determining the level of company's exposure from its product's ingredients, suppliers, etc.
- Eric Berg, Director of Supplier Quality for Amgen recommended, *The Black Swan,* a book suggesting that the bulk of risks comes from *outside* the risk model you may have created.
- For critical materials extra testing obtained from a new supplier, extra tests (i.e., NMR, CE, NIR), site visits and routine monitoring is probably required. For example in such a case the presenter from Pfizer said that staff would visit the supplier's plant once a month. Other examples are given in the slides attached. Plants in emerging markets may warrant being rated "higher risk."
- Amgen lists their suppliers as preferred, standard and marginal. The latter two require closer monitoring according to Amgen.
- As part of risk assessment, determine if you need to audit the supplier's suppliers.
- ICH 10 section on "Knowledge Management" requires a firm to "surface" emerging issues.

3. Auditing/Auditors

- In emerging markets, the audit may need to include someone (ex-FBI agents were mentioned) to assess the security of the site, in regards to opportunities to cheat, etc.

The presenters emphasized that companies should not wait until the perfect system (either international consortium or company-based) is created.

- Audits must do more than simply look at GMP compliance. They must include a critical look on supply chain controls. Ask questions: What happens to the API/excipient when it leaves the site? How will it/does it arrive at my company? What about the deviations and changes that can affect my product? What about the quality of the Drug Master File or Excipient Master File?
- Auditors should be aware of and prepared for differences in language and culture, i.e., they may need independent translators familiar with the country's culture to join the audit team to be better able to check for truthfulness of interview responses.
- Value of the audit is questionable if the audit is only one or two days long. Two presenters suggested five day audits in order to get a true sense of the responsibility of the supplier.
- Determine if there is a strong quality culture at the site, i.e., the commitment to do things right *everytime*
- Third party audits were recommended by Amgen because it frees up resources to work more with the suppliers.
- In emerging markets, companies must confirm that the site being audited is not a "shadow" company, (i.e., a new "nice looking" site that in fact does *not* actually make the API or excipient you are expecting to be made there). Request shipping records, plant capacities, label reconciliation's, and reaction yields, etc. to help confirm the material is actually made at that site.

4. Analytical Techniques

- Avoid nonspecific ID tests on composite samples.
- Consider adding extra, more sensitive tests to check for possible/likely contaminants. One example given was replacing the simple USP protein test with one designed to look for melamine, a contaminant recently discovered in baby and pet foods.
- Review and approval by in-house experts on the data on identity, such as NMR (for organics) and mass spec, for brand new synthetic materials.
- Look at and test *every* container of a critical or high risk material, i.e., heparin, sorbitol, glycerin and propylene glycol (the latter two which might contain the chemically similar diethylene glycol).
- Perform at least one specific ID test and implement periodic testing to confirm accuracy of COA's, per 211CFR211.84(c).

5. IPEC

- Published a guide to Good Disposition Practices (GDP) in 2006, and is available at IPEC website.

- Proposing an "Excipient Information Protocol" rating that a supplier would get after passing a third party audit. Once the supplier was rated, the company can then potentially avoid repeat audits.
- Published proposed "Excipient GMP's" on their website
- Created International Pharmaceutical Excipients Auditing (IPEA) in 2000 as a subsidiary to provide third party audits of excipient suppliers; audits will be made available to all pharmaceutical companies for a fee. So far 30 audits have been completed by their trained and qualified auditors. Baxter is partnering with them (i.e., helping pay for audits), along with two other firms. IPEA is seeking accreditation from the American National Standards Institute (ANSI) by June 2009.
- Signed a Memorandum of Understanding in September 2008 with the European Fine Chemicals Group (EFCG) to develop jointly a certification program for manufacturers and distributors of pharmaceutical excipients. The EFCG has proposed creating a classification system for excipients, based on use (i.e., solid dosage, parenteral). EFCG is looking to conduct a stakeholder workshop in early 2009.

6. Reduced Testing

- Should not simply be based on "first three" or "first ten" lots received. Do not be on autopilot.
- Need a feedback loop. Increase testing and monitoring based on supplier scorecard and environment (see Environment section).

7. Contamination Possibilities

- When suppliers purposely take material low in an allowed "excipient," for example chloride, and mix in a greater amount of it up to the limit in order to realize a greater profit. The same would be true of adding to an API an allowed "excipient" to reduce but not go below the assay limit (i.e., dilute material from 102.0% to 99.5%.).
- Be on the look out for suppliers blending in rejected product into a lot of acceptable product.

8. Environment

- Establish a surveillance team that monitors the news and geopolitical events that may cause disruption in supply and possibly provide incentives for counterfeiting and diversion of your supplies.

9. Quality Agreement

- IPEC has example templates on their website
- The Pfizer representative said that the company is moving to obtain quality agreements for all suppliers.

10. Quality Control/Assurance

- Must focus on quality, not on the regulations.

11. Compendial

- Remember that compendial monographs do not address purposeful, unexpected or accidental contamination or cross contamination. Extra tests and procedures (i.e., GMP, GDP, etc.) may be needed to ensure against this (i.e., the old mantra that "you can't test in quality").

Take Home Messages

The presenters emphasized that companies should not wait until the perfect system (either international consortium or company-based) is created. Start doing incremental change *now.*

The following are good take-home messages from the conference:

1. Put together a list of suppliers and the countries where they are located. Perform a risk assessment based on location and the criticality of the API or excipient supplied.
2. Set up a task force to revise API/excipient specifications to include photos of labels and containers.
3. Immediately consider adding extra scrutiny (analytical testing, QA monitoring) to known high-risk compounds.

And in the words of **Joel Barker**, whose call to action was quoted by of **Edwin Rivera-Martinez,** Chief, Manufacturing Assessment and Pre-approval Compliance Branch, Office of Compliance, CDER, FDA:

Vision without action is only a dream. Action without vision just passes the time. Vision with action can change the world.

About the Author

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Drug Supply and Distribution

Part 1: Audits of Suppliers of Computer Products and Services

Chris Ward, SynTegra Solutions, and Thomas Menighan, APhA

The people who manufacture, distribute and handle pharmaceutical products and provide services are only human and can make mistakes. Audits provide diligence in the oversight of all processes including background checks in hiring and management practices. Auditing the supply and distribution system is just one step to eliminate as many points as possible for failures where counterfeit or diverted products may find their way into the hands of patients.

[Note: One of the goals of examining audit resources in this article is to provide an overview of processes and procedures for auditing in the regulated environment. In Part 2, we attempt to show the breadth and depth of the standards to which those involved in the discipline are, and should be, held.**]**

In 1996, the U.S. FDA challenged the industry to establish a standard way to assess the structural integrity of acquired computer software as well as lower overall costs to the industry.

Auditor Resources

The following organizations train or qualify auditors, maintain credentials or set standards for these professionals.

American Society for Quality (ASQ)
www.asq.org

International Register of Certified Auditors or IRCA
www.irca.org/home.html

European Commission on Enterprise and Industry (Pharmaceuticals)
ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/anx11en.pdf

Parenteral Drug Association
www.pda.org

In 1997, a task force was formed to assess the integrity of and develop a guideline for auditing acquired Commercial Off the Shelf (COTS) software. Under the umbrella of the PDA's Computer Validation Interest Group, the PDA along with the FDA, members of the user community from the pharmaceutical and medical device industries, and the software developers themselves came together to create and publish a guideline (*PDA Technical Report No.32, Revised, Auditing of Suppliers Providing Computer Products and Services for Regulated Pharmaceutical Operations*) for auditing the acquired computer software and services.

The objectives of this Task Group were focused on the specific application of software in the manufacturing process. These objectives were very similar to those that any group of professionals from any sector of the industry meeting to establish standards might have. They include:

- Define and demonstrate a process for supplier audits and qualification in a way that promotes standardization and simplification
- Meet regulatory expectations for structural integrity of acquired software and computer products in general (regardless of where in the manufacturing process they were applied)
- Satisfy customer needs for information as supporting procurement, systems engineering and computer validation
- Lower costs to both the pharmaceutical companies and suppliers

With regard to the latter point, costs of vendor and supplier audits within the industry have increased and pharmaceutical companies may incur costs (internal and external) upwards of $750,000 a year to perform, manage and archive audits. Examples exist that show reductions in cost greater than 50% through the use of a central repository. Such a repository was created by the PDA and is now known as the Audit Resource Center, or ARC.

In the process of developing the published audit process, the PDA TR-32 Task Force performed research and used their experience from supplier audits to draft a common practice to meet the needs of the industry. The needs assessment came from the users' agreement that auditing practices used throughout the industry were cumbersome, duplicative and inconsistent.[1] Standards for these practices are developed by organizations that include members who work in the industry and governing bodies such as the FDA and the EMEA.

Anyone who manufactures products that are regulated by the FDA must conduct an assessment or due diligence of their vendors, typically in the form of audits. In this environment, those vendors who produce equipment that utilizes software or those suppliers who develop software itself have to be audited and a well accepted process often used is TR-32.

Other guidelines and standards exist to support professionals in their auditing, examination, and inspection of manufacturing processes and technologies such as clean rooms, controlled environments and product pedigree in the chain of custody.

Good Automated Manufacturing Practices or GAMP 5 is used as an audit guide for many manufacturing processes where computer products and software are not the primary process being examined, like controlled environments. Like TR-32, GAMP 5 is also enhanced, refined and restructured, to reflect current regulatory expectations and good practice. Professionals from North and South America, as well as Europe contributed to the production of GAMP 5 which is intended for suppliers and users in pharmaceutical manufacturing

and related healthcare industries. This guide draws together key principles and practices and describes how they can be applied to determine the scope and extent of validation for different types of automated systems.[2]

Benefits of this standard to industry users and suppliers echo those of the TR-32 and include:

- Cost benefits, aiding the production of systems that are fit for this purpose, meet user and business requirements and have acceptable operation and maintenance costs
- Increased understanding of the subject and introduction of a common language and terminology
- Reductions in cost and time taken to achieve compliance systems, and clarification of the division of responsibility between user and supplier
- Audits have historically been executed by compliance personnel in pharmaceutical companies who possessed a basic knowledge of software or other processes. These knowledgeable individuals used methods and checklists common to auditing physical processes and checking paper trails. Much of this was based on written regulation for good manufacturing and clinical practices, but was not always suited for technology processes.
- Audits conducted by independent auditors to a standard are valued by industry as a way to "certify" that a vendor or company has followed the proper procedures and their work or products have been through a 3rd party review and are credible.
- Training, qualification and certification are ways for developing personnel and teams that can execute audits with the latest standards from governing organizations and professional associations like PDA, the American Society for Quality(ASQ) and others. The ASQ has developed several training and certification courses relevant to this discussion.[3]

Third party participation in the audit process creates some distinct advantages. A 3rd party resource can be a credible source for information for participation by technical experts, for overview from sanctioning bodies and resource extension for valuable and scarce internal resources.

One such resource to auditing is a central repository for audits, and reports on audits, that can be shared across the enterprise and throughout the industry by both a customer and their vendor in an effort to strengthen a vendor relationship, reduce time and cost associated with the auditing process and provide quality control for documentation.

Many organizations may have processes and even specific software for managing audit data and reports. Like internal audit systems and those personnel managing them, they may be subject to the individual needs of groups within the company or department and thus, may not meet a set of standards or standard practices.

The same bodies that develop and maintain standards also devise ways to help maintain the integrity of the reports and information produced by an audit in an effort to make it acceptable to multiple stakeholders with the organization or across the industry.

One such entity is the Audit Resource Center (ARC), which was, created by the PDA's task group and managed under the supervision of the Audit Guidance Advisory Board, an advisory board within PDA. The ARC provides audit reports to the industry and partners with suppliers of software products to facilitate independent audits using the TR-32 Audit Process. The ARC maintains the integrity and quality of submitted audits as well as the auditors who conduct them. These audits are made available to manufacturers who need them as part of the due diligence process described above.

This article is not intended to be an exhaustive journey through the history, development or practice of technical auditing within the regulated pharmaceutical industry, but rather to illustrate some current resources available within particular sectors and to provide perspective on audit practices that consume many hours for all of the professionals who spend careers dedicated to the pursuit of quality.

About the Authors

Chris Ward is the Director of the Audit Resource Center for SynTegra Solutions. He is responsible for business development and management of the ARC database of software process audits. He began his career in sales and has broadened his experience with work in human resources, sales training, management development and more recently, marketing. He spent much of his career with Rhone-Poulenc Rorer Pharmaceuticals, and then worked for Amgen as a product manager in the Nephrology Franchise and worked on the launch of Aranesp.

Thomas Menighan is new Executive Director, CEO designate for the APhA. At the time he authored this article, he was the President of SynTegra Solutions, Inc., where he lead development and delivery of a full suite of operational and regulatory compliance services for pharmaceutical and biotechnology companies from product discovery to distribution. He was the former CEO of SymRx, Inc., a pharmaceutical information technology company that developed CornerDrugstore.com and was sold in 2002.

References

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2. GAMP 5: Enabling Innovation and Technical Advance – One Day Quick Start – the Best Presentations from the GAMP 5 Launch (E05); ISPE Website, 2008
3. Auditing and ISO Solutions, Quality in Manufacturing. American Society for Quality. 04 Aug 2007. www.asq.org

Quality & Regulatory *Snapshot*

Interest Group *Briefing*

A Discussion With Two IG Leaders

Emily Hough, PDA

Mike Long is the leader of PDA's Quality Risk Management (QRM) Interest Group, which was formed in late 2008. **Anders Vinther,** PhD, became the new leader of PDA's Quality Systems (QS) IG in 2008. Both answered a few questions about their respective IG's for the *PDA Letter.*

Long, Director Engineering and Product Development, CooperSurgical, said that the only problem he sees so far with the QRM group is its "size." He said that that challenge would be combated by introducing sub-teams to work on specific products.

Long also said that he thinks the IG is important as it will serve to clear up any confusion industry members have about QRM, and find ways to fully integrate QRM into industry's routine business processes.

Future plans for the IG include a meeting at PDA's Annual Meeting and pairing members of the group with specific efforts, e.g., task force, chapter meetings, technical report and or journal articles. Long said long-term, the goal of the group is to create a strategic vision for the group; align the needs of the members with the goals of the Board and SAB; create a workable management plan; initiate at least one task force for a new technical report and publish at least two risk related journal articles.

A Board member for PDA and new leader of the QS IG, Vinther, Senior Director, Corporate Quality System and Support, Genentech, says he makes the time to chair the group as it relates to his area of expertise, and that "the interest group is a great place to share better practices and discuss challenges with industry and regulatory agency colleagues."

Vinther would like the IG to work on topics related to the implementation of ICH Q10, as such, a key topic would be "Knowledge Management," and how industry captures key knowledge about products and processes and becomes less dependent on "tribal knowledge" and more integrated into the Quality System. Vinther added that at QS IG's next meeting at the PDA Annual Meeting, he would like to discuss how Quality Systems should continue to be improved to help ensure a safe supply chain.

Check out these and other IG's out at PDA's Annual Meeting. Visit www.pda.org/annual2009 for the agenda. Hope to see you there!

Health Authority *Special Report*

Israel Joins PIC/S

Karen Ginsbury, PCI Pharmaceutical Consulting

On November 12, 2008, Israel's Pharmaceutical Inspectorate was unanimously voted to join the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Israel's membership with the organization became effective on January 1, 2009. As a member of this organization numbering 36 participating authorities, Israeli inspections will now be mutually recognized and shared with other members on a voluntary basis. For many manufacturers in Israel this provides the practical benefit of less inspections, since many of the countries that previously sent inspection teams will rely on the PIC/S membership and the Israeli Health Ministry inspections.

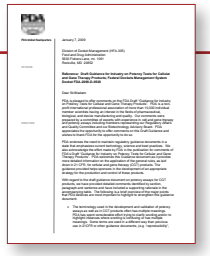
Ministry officials **Mimi Kaplan,** PhD, Director, Institute for Standardization and Control of Pharmaceuticals Pharmaceutical Administration, and **Rami Kariv**, PhD, Head, GMP Inspectorate, updated industry at the PDA Israel Chapter meeting, on December 10, 2008 at David Intercontinental in Tel Aviv. The two officials focused on Israel's new involvement with PIC/S and the status of intensive talks with the European Union regarding signing an Agreement on Conformity Assessment and Acceptance of Industrial Products (ACCA). The negotiations with the EU authorities have become feasible due to the new pharmaceutical GMP Israeli legislation which has been recognized to be equivalent to that of the EU after making some additional amendments.

With respect to inspections, the EU is willing to accept the Israeli inspections because it joined PIC/S and the two processes go hand-in-hand. The ACCA is expected to be signed during 2009, and one of the biggest advantages of this is that Israeli companies exporting to Europe will no longer need to perform additional testing in an EU certified laboratory.

[Editor's Note: France's Agency for Veterinary Medicinal Products also became a member of PIC/S on January 1, 2009.**]**

PDA Urges Alignment with ICH in Comments on U.S. FDA Potency Test Guide

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



January 7, 2009

Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Reference: Draft Guidance for Industry on Potency Tests for Cellular and Gene Therapy Products; Federal Dockets Management System Docket FDA-2008-D-0520

Dear Sir/Madam:

PDA is pleased to offer comments on the FDA Draft "Guidance for Industry on Potency Tests for Cellular and Gene Therapy Products". PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in cell and gene therapy and potency assays including members representing our Regulatory Affairs and Quality Committee and our Biotechnology Advisory Board. PDA appreciates the opportunity to offer comments on this Draft Guidance and wishes to thank FDA for the opportunity to do so.

PDA endorses the need to maintain regulatory guidance documents in a state that emphasizes current technology, science and best practices. We also acknowledge the effort made by FDA in the publication for comments of FDA's Draft "Guidance for Industry on Potency Tests for Cellular and Gene Therapy Products". PDA welcomes this Guidance document as it provides more detailed information on the application of the general rules, as laid down in 21 CFR, for cellular and gene therapy (CGT) products. The guidance provided helps sponsors in the development of an appropriate strategy for the production and control of these products.

With regard to the draft guidance document on potency assays for CGT products, we have provided detailed comments identified by section, paragraph and sentence and have included a supporting rationale in the accompanying table. The following is a brief overview of the major points that PDA believes are most important to highlight to strengthen this guidance document:

- The terminology used in the development and validation of potency assays as well as in CGT products often has multiple meanings. PDA has spent considerable effort trying to clarify wording and/or to highlight instances where wording is confusing or has multiple meanings. Some terms are used in a different way than previous use in 21CFR or other guidance documents, (e.g. "reproducibility" and "sensitivity"), or terms are used which are not defined in this or other documents, (e.g. 'reliable' assay appropriate for lot release; strength vs. potency). Some clarification about the use of specific terms in this Guidance document are provided in footnotes, however it is proposed to add a Section 'Glossary' to collect all definitions in a single place (rather than in footnotes) and to clarify the intended meaning of terms in relation to CGT potency assays.
- The term "reproducibility" is used several times in 21CFR and those uses are referred to in this Guidance, but the term is never defined. PDA feels it would help the reader of this document to define "reproducibility" as it pertains to uses in this document, especially where it varies from the definition provided in ICH Q2(R1); i.e. with regard to qualitative assays. Because Q2(R1) refers to reproducibility as one of three aspects for characterizing assay precision, PDA recommends careful use of the term in accordance with Q2(R1). Where it seemed appropriate, PDA substituted the words "intermediate precision" for "reproducibility".
- PDA feels that it is important for FDA guidance documents to be consistent with ICH documents and supports the efforts of regulators and industry to harmonize these documents. We urge the FDA not to ask for validation of parameters not called for in ICH Q2(R1), e.g. sensitivity in IV.C.1 and IV.C.3.

Again, PDA appreciates the opportunity to comment on this draft Guidance document and provides these recommendations for your consideration. PDA believes that these comments will clarify and strengthen the Guidance document to better serve the needs of both regulators and industry.

We would be pleased to offer our expertise in a public discussion and/or meeting with FDA to provide clarification of our comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely

Robert B. Myers
President, PDA

Regulatory Briefs

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

North America

Draft Guidance Available on Assay Migration Studies in Regards to In Vitro Diagnostic Devices

A draft guidance entitled, *Assay Migration Studies for In Vitro Diagnostic Devices is now available. The draft guidance* presents a least burdensome regulatory approach to gaining Agency approval of Class III or certain licensed in vitro diagnostic devices in cases when a previously approved assay is migrating (i.e., transitioning) to a new system for which the assay has not been previously approved or licensed.

Comments should be received by April 6, 2009.

OTC Guidance Available

A guidance for industry entitled, *Labeling OTC Human Drug Products - Questions and Answers is now available*. This guidance is intended to assist manufacturers, packers and distributors of OTC drug products in complying with the Agency's regulation on standardized content and format requirements for the labeling of OTC drug products.

Comments Welcomed on PDUFA Pilot Project Proprietary Name Review

An opportunity to comment on a proposed collection of information relative to the PDUFA Pilot Project Proprietary Name Review is now available.

This relates to the concept paper the U.S. FDA published in October 2008, describing how pharmaceutical firms may evaluate proposed proprietary names and submit the data generated from those evaluations to the Agency for a review under the pilot program.

Comments on the collection of information should be submitted by February 23, 2009.

Medical Device Submission Guidance Published

An industry guidance entitled, *Modifications to Devices Subject to Premarket Approval (PMA) – the PMA Supplement Decision-Making Process* is now available. The purpose of the guidance is to help industry determine the type of regulatory submission that may be required when a device subject to PMA is modified.

Expiration Date Extended in Compliance Policy Guide

The expiration date for a compliance policy guide entitled, *Radiofrequency Identification (RFID) Feasibility Studies and Pilot Programs for Drugs,* is being extended to December 31, 2010.

The guide describes how the U.S. FDA intends to exercise its enforcement discretion regarding certain regulatory requirements that might otherwise be applicable to studies involving RFID technology for drugs.

Commenting Opportunity on Proposed Collection of Information on U.S. FDA's Medical Device Recall Authority

There is an opportunity to comment on a proposed collection of information relating to the U.S. FDA's Medical Device Recall Authority.

The information collected under this recall authority will be used by FDA to ensure that all devices entering the market are safe and effective. If problems are detected with medical devices, that are deemed dangerous or defective they will be removed immediately from the market.

Comments are to be submitted by February 17, 2009.

Draft Guidance on Devices Labeled as Sterile Available

A draft guidance for industry is available, entitled, *Submission and Review of Sterility Information in Premarket Notification Submissions for Devices Labeled as Sterile*; this draft guidance updates and clarifies the procedures for reviewing premarket notification submissions [510(k)s] for devices labeled as sterile, particularly with respect to sterilization technologies the U.S. FDA considers novel, and the information that should be included in 510(k)s for devices labeled as sterile.

Comments should be received by March 12, 2009.

Guidance on Orally Disintegrating Tablets Available for Industry

The U.S. FDA has announced the availability of a guidance for industry on orally disintegrating tablets. The guidance provides pharmaceutical manufacturers of new and generic products with an agency perspective on the definition of an orally disintegrating tablet (ODT) and also provides recommendations to applicants who would like to designate proposed products as ODTs.

U.S. FDA Seeks Comments on Postmarketing Adverse Events

The U.S. FDA invites comments specifically on the following topics pertaining to postmarketing adverse events. The proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; ways to enhance the quality, utility, and clarity of the information to be collected; and ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Comments may be submitted until February 17, 2008.

2009 PDA/FDA Joint Regulatory Conference

Securing the Future of Medical Product Quality: A 2020 Vision

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

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

www.pda.org/pdafda2009

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

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

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

Calibration and Qualification of Equipment and Systems Discussed at PDA Israel Event

Ilana Zigelman, MPH, BiolineRx

On November 18, 2008, the PDA Israel Chapter held a one day technical seminar for about 60 participants on "Calibration and Qualification of Equipment and Systems in the Pharmaceutical Industry."

Opening comments were delivered by **Raphy Bar**, PhD, President of the PDA Israel Chapter.

Arnan Ben David commenced with a practical discussion about calibration in the view of the recent GMP requirements. Arnan discussed regulatory requirements for calibration in the United States and Europe, instrument criticality, calibration procedures including frequency and methodology, certification, deviations and allowed tolerances.

The next speaker was **Teddy Hoffman.** He presented "Basic Requirements From in House and External Calibration Laboratories." Teddy talked about traceability, causes of uncertainty, industry and regulatory legal metrology requirements and ISO/IEC 17025's "Management System" and "Technical Requirements." He discussed the requirements for documentation of calibration including the elements that must be, may be or must not be on the calibration certificate, status identification and application of the equipment, specification setting and application, calibration frequency and review of contracts.

After the coffee break we returned to an informative presentation by **Mordechai Izhar,** PhD, on regulatory aspects in "Qualification of Equipment and Systems-Current Regulatory Requirements." Mordechai discussed various guidance documents and their individual distinctions including:

- *Pharmaceutical GMP's for the 21st Century, A Risk Based Approach – Final Report* which corresponds to *ICH Q9: Quality Risk Management* (EU Guidelines to GMP's Volume 4, Annex 20). These call for science-based policies to help the U.S. FDA meet their goal to enhance and modernize the regulation of pharmaceutical manufacturing and requires quality risk management as an integral part of a manufacturers quality system.
- *The Quality Systems Approach to Pharmaceutical cGMP Regulations* to help manufacturers meet requirements of the FDA's GMP regulations using a comprehensive quality systems approach.

Limited manufacturing control methods, process and system complexity and limited analytical capacity are the main contributing factors to process variability and process understanding.

- *ICH Q10: Pharmaceutical Quality System*, which describes management responsibilities towards the use of science and risk based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product life cycle.
- *ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* which specifies all utilities that could impact on product quality.

He also discussed the aims of qualification and validation including uses of a validation master plan and finished up with a summary of current regulatory requirements for qualification of equipment and systems.

Ronen Sarusi gave a technical presentation on "ASTM E2500-07 Standard: A New Approach for Commissioning & Qualification of Equipments and Systems." He also discussed the new ISPE draft guide entitled, *ISPE Baseline Guide: Volume 5 – Commissioning and Qualification.* Ronen explained that the standard is necessary since the qualification has become an expensive time consuming document-intensive process that adds little value in terms of ensuring equipment is fit for use. According to him, we can reduce these costs and be more effective through, use of risk assessment practices, focusing on aspects critical to the patient, managing duplication of testing done by the equipment manufacturer and end user. Ronen reviewed key aspects of the ASTM and ISPE guide and presented case studies as well.

The next speaker, **Yehoshua Aloni,** PhD, introduced us to the qualification of bioreactors. He began his presentation with an introduction to the contemporary issue of the molecular complexity of biotech product. Yehoshua then discussed the subject of fermentation including the biotechnology production process and mode of operation, batch production versus continuous production including scale up and qualification issues. He highlighted various types of bioreactors like the fermentor/bioreactor for pilot scale, large bioreactors for bacterial and mammalian cells and the required utilities for the industrial bioreactor. Limited manufacturing control methods, process and system complexity and limited analytical capacity are the main contributing factors to process variability and process understanding.

Also discussed were methods to improve manufacturing control including use of quality by design, product specifications based upon mechanistic understanding, continuous improvement and assurance of quality, and online monitoring and data logging. He finished with a review of the benefits of disposable systems regarding system qualification.

Ido Cohen gave his presentation on "A Practical Approach to Programmable Logic Controllers and Human Machine Interface Validation" within the biopharmaceutical and pharmaceutical environment. The approach is based on implementing validation throughout the project life cycle, from planning through specification development including performance of a hazard study via use of Computer Hazard and Operability. Emphasis was given to the planning phase which is important for determining the scope of validation, responsibilities, technical requirements and the final outcome. Specific guidance was given on common practices for writing validation plan, user and functional requirements, reliance on suppliers, test protocols, audit plan, implementing requirements for software and hardware and testing for release.(Professionals involved in any of the above life cycle phases may find these practices as helpful.)

Eitan Gross concluded with an interesting presentation on the "Qualification of Heating, Ventilating and Air Conditioning (HVAC) Systems." This presentation reviewed the definitions relevant to HVAC qualifications including the controlled area versus the critical area qualification models and planning for critical and non-critical systems qualification, critical and non-critical components, models for direct and indirect impact systems and impact assessment. Eitan reviewed prequalification and qualification documentation requirements including the User Requirement Specification and the Validation Master Plan. According to him, practical aspects of design qualification, installation qualification, operation qualification, design qualification and process qualification, as well as ongoing process control including periodical requalification help to assure a state of control including periodical requalification.

PDA's *Who's Who*

Yehoshua Aloni, PhD, Bioprocess Technologies Israel Biotech R&D, Teva

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

Arnan Ben-David, Strategic Projects Director, Management, Omrix

Ido Cohen, Director of Engineering Protalix Biotherapeutics

Eitan Gross, QA & RA Director, Medimop Medical Projects

Teddy Hoffman, Consultant, Israel Laboratory Accreditation Authority

Mordechai Izhar, PhD, Manager, Validation Department, Ludan Engineering

Ronen Sarusi, Industrial Compliance Manager, Teva

PDA Israel Chapter's Annual Meeting Covers Latest Health News

Karen Ginsbury, PCI Pharmaceutical Consulting

The PDA Israel Chapter's Annual Meeting, held December 10, 2008, featured a discussion of the recent acceptance of Israel's Pharmaceutical Inspectorate, a division of the Israel Ministry of Health into the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Two members of the Isreali Ministry of Health, **Mimi Kaplan,** PhD, and **Rami Kariv**, PhD, provided in-depth analysis of the impact of the PIC/S decision on Israel's Inspectorate. **[Editor's Note:** See "Health Authority Special Report" for more information on Israel's Pharmaceutical Inspectorate joining PIC/S in this issue's Quality & Regulatory Snapshot, p. 24.**]**

The annual meeting, held at the David Intercontinental in Tel Aviv, opened with **Raphy Bar**, PhD, and PDA Israel Chapter President, welcoming guests and was followed by **Karin Baer,** PDA Israel Chapter Treasurer, providing a financial report.

A lecture on the National Health Basket—Israel's list of medicines and technologies covered by government's health insurance—was provided by Advocate **Yoel Lipschitz**, who sits on an important committee responsible for deciding which technologies and new medicines are added to the basket each year.

The lecture discussed conflicts and interests and presented the ethical dilemmas involved in choosing novel therapies to be added to existing therapies. This fascinating presentation described how with the introduction of the National Health Law in 1994, a vision of "justice, equality and mutual help" was envisaged for every citizen of Israel. The main problem, as in most countries around the world, is rationing and gate-keeping as well as the cost of prescription drugs which increases around 10% each year. There are several dominant players in the field each pushing their particular interests the primary players being Health Maintenance Organizations (HMOs) of which there are four; hospitals, doctors, pharmacists and the pharmaceutical companies who are interested in pushing their particular therapies.

The Ministry of Health sees itself as a kind of watchdog, filtering different requests and ensuring fair play, and the oversight committee includes members of the public, ethicists as well as specialists in different fields of medicine. Updating the National Healthcare Basket requires clinical, economic and technological-epidemiological evaluation but inevitably any decision has social, ethical, political and legal aspects. The conclusion was that the process is not a bad one, although it could have increased transparency. There will always be a certain element of manipulation by Pharma companies as well as a chronic shortage of funds that translates to around 400 effective medicines waiting to enter the basket. The presentation tied the research and development efforts that participants are all too familiar with; the target patient profile and their needs and vulnerabilities. It is these reminders that bring industry closer to their customer.

The subsequent presentation addressed academic research and presented a case study for taking an idea and translating it by focused development into an effective pharmaceutical product. **Abraham Rubinstein** described how an article that appeared in *Science* in 1986 addressed oral delivery of insulin and other peptides by wrapping them in a polymer that would dissolve in the large intestine. This idea was developed by Abraham and a team of scientists in close collaboration with a pharmaceutical company (Perio Products Ltd, now Dexcel Pharma) to develop implants and drug delivery systems for molecules that previously had never been considered as candidates for oral administration. The presentation emphasized elements of pharmaceutical research and development, and in particular how collaboration between academia and industry can result in rapid realization of useful ideas once again benefiting the end-user i.e., the patient.

This author ended the evening with an update on hot topics, including issues that have been on the agenda of PDA's Regulatory Affairs and Quality Committee (of which she is a member), including the ballots on comments submitted for the following regulatory documents:

- U.S. FDA Draft Guidance for Industry Residual Solvents
- Phase I GMP Guidance and Final Rule
- U.S. GMP revisions
- Draft Guidance for Industry – Parametric Release
- Annex 13 – EU GMPs
- Annex 11 and Chapter 4 – EU GMPs
- Process Validation draft guidance
- *Draft Guidance for Industry: Potency Determination Cellular and Gene Therapy Drug Products*

The evening ended with a festive dinner and participants headed home with a pleasantly full head and stomach!

PDA's *Who's Who*

Karin Baer, Quality Assurance Director, Quality Assurance, Omrix-Biopharmaceuticals and PDA Israel Chapter Treasurer

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

Mimi Kaplan, PhD, Director, Institute for Standardization and Control of Pharmaceuticals Pharmaceutical Administration, Israeli Ministry of Health

Rami Kariv, PhD, Head of GMP Inspectorate, Israeli Ministry of Health

Yoel Lipschitz, Deputy Director-General, Regulation of Health Management Organizations and Supplementary Insurance Programs, Israeli Ministry of Health

Abraham Rubinstein, Professor, Pharmaceutical Sciences, The Hebrew University of Jerusalem

PDA
Parenteral Drug Association
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PDA Europe Update on

Pharmaceutical Ingredient Supply Chain

10-11 March 2009
Munich, Germany

Conference/Exhibition: 10-11 March
Training Course: 12 March

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

Register by 10 February and SAVE!

The PDA Europe Pharmaceutical Ingredient Supply Chain Conference will provide a European focus regarding scope of the issues and problems, perspectives from stakeholders, and potential activities to reduce supply chain risks to pharmaceutical manufacturers and suppliers.

PDA UK Chapter Tours Ispen Biopharm

Mike Baker, Pharma Quality Consulting

On October 16, 2008, a meeting on new developments in lyophilization initiated by PDA's UK Chapter, was hosted by Ipsen Biopharm at its Wrexham, UK site. After welcoming the Ipsen personnel and PDA members attending the meeting, the Ipsen Biopharm VP and Site Director gave an overview of the company, the site and the background behind construction of Unit 12—their new £40 million aseptic filling and lyophilization facility.

The Biofill/Dysport Production Manager, then gave the keynote presentation on new developments in lyophilization, focusing on sterilization aspects. Concluding the more formal part of the meeting, the Head of Engineering presented an overview of Unit 12—Ipsen Biopharms new state-of-the-art facility for the aseptic filling and lyophilization of vials.

Attendees then had an opportunity to tour round the new facility. Unit 12 is in the advanced stages of construction and provided a perfect opportunity to "get up close and personal" with the advanced technology in the building, for example, the integrated and isolator based line which will be used for filling, lyophilizing and capping vials.

The event ended with informal discussions between attendees, presenters, tour guides and organizers, over an excellent buffet provided by the company. PDA members were unanimous in their opinion that the event had been very well worthwhile attending. Many asked about future events, including the possibility of a return visit to Ipsen Biopharm, when the facility is fully operational.

In closing the meeting and on behalf of PDA, I thanked all those at Ipsen Biopharm who had willingly given their time and made this a very successful event—the presenters and particularly the Head of Security and Site Services played a key role in its organization.

PDA Mountain States Chapter Event and Speaker Dinner a Hit

Keith Bader, JM Hyde Consulting

The 2008 PDA Mountain States Chapter vendor show and speaker dinner was held at the Renaissance Hotel in Broomfield, Colo. on October 2, 2008. The Chapter chose a new, more central location than previous events to increase attendance, resulting in one of their best meetings yet, with 93 attendees and 13 vendors represented.

As part of an effort to encourage new membership to the Chapter, the attendance of three students from local universities was sponsored by Global Quality Alliance Consulting and Extronex. In addition, the PDA Mountain States Chapter continued their commitment to fostering regulatory and industry interaction through the sponsorship of a booth for the Denver district office of the U.S. FDA which was manned by **Devin Koontz**, Public Affairs Specialist and **Mike Goga,** Investigator.

Dave Mulligan, Consultant, our speaker for the evening, was an investigator with the FDA from 1972 to 1991. As a lead FDA Investigator and Compliance Officer for the Barr Labs inspections and resulting trial, Dave testified as the sole expert government witness. The trial resulted in the "Wolin Decision" which has had a major impact in the areas of drug testing and retesting, process validation, blend sampling, and failure investigations. The topic was of great interest to regional Chapter members and initiated discussion both during and after the presentation. Special thanks go to RMC Pharma as an event sponsor.

Vendors attending the event:

Acceleration, LLC
Berkshire
Biolog
Commissioning Agents, Inc.
Extronex
General Physics Corporation
Global Quality Alliance
Lonza
Hyde Engineering + Consulting
Regulus Pharmaceutical Consulting
Remel (Thermo-Fisher Scientific)
Rommelag, USA, Inc.
Quality Systems Integrators

Volunteer Spotlight

Michael Anisfeld

Senior Consultant, Globepharm Consulting

Education: MSc, Pharmaceutical Technology, London University; MBA, Lake Forest College

PDA Join Date: January 1976 (within a week of immigrating to the USA)

Areas of PDA Volunteerism: Board of Directors; RAQC, SAB, Publications Committee (member); TR-2 Task Force (Chair); meeting and course speaker; PDA Journal author; Midwest Chapter (past President)

Professional Awards Won: GMP Auditor Hall of Fame - GMP Institute

Interesting Fact about Yourself: For the past 10 years, I have donated four weeks of my time annually without charge to improving the quality of pharmaceuticals in third world countries. I have lectured on GMP topics to government and industry in developing countries and trained government GMP inspectors how to perform effective GMP inspections. I have been invited by governments to lecture in Bangladesh, Cuba, China, Ethiopia, Ghana, Jamaica, Kenya, Mongolia, Nigeria, Sri Lanka and Vietnam. I find it such an honor, at my stage in life, to be afforded the opportunity to give back to those with the greatest need who can least afford to provide pharmaceuticals for their populations and to raise the quality of the drugs they produce.

I think that it is true to say that ***everything I am professionally today*** *can,* ***in large measure,*** *be traced to* ***my involvement in PDA.***

Why did you join PDA and start to volunteer? Selfishly at first, as a way to learn about United States pharmaceutical GMP practices. I was a new immigrant in 1976 (coincident to the introduction of the draft GMPs in the USA). As time went on, I found that my experiences and perspectives, having worked overseas to British GMP standards (which had been introduced six years earlier than the U.S. GMPs) were of use to my American colleagues, and my participation in PDA became, for me, a GMP dialog.

Of your PDA volunteer experiences, which stand out the most? Without question, participation as a member or leader of PDA technical committees. The learning and networking that occurs as a PDA volunteer is stimulating and enriching. I can only hope that I have contributed as much as I have learned from PDA over the past 30 years.

How has volunteering through PDA benefited you professionally? I think that it is true to say that everything I am professionally today can, in large measure, be traced to my involvement in PDA.

Which member benefit do you most look forward to? Receiving the *PDA Letter*—as a professional association publication I consider it an *immediate must read* material. I cannot say that about any publication I receive from any of several other professional associations that I belong to.

Which PDA event/training course is your favorite? Hard to say—I learn something from each conference and event I attend, both at the national and regional (Midwest) levels.

What would you say to somebody considering PDA membership? If you work in the pharmaceutical industry, then technically PDA is "the" organization to keep your technical skills up-to-date; and as a side-benefit, the networking opportunities cannot be beat. I have never for a day, during my over 30 years of membership, regretted belonging, or begrudging my annual membership fee.

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

Chapter Contacts

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

Asia-Pacific

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Contact: Robert Caunce
Email: robert.caunce@hospira.com
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Please Welcome the Following Industry

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Valeria Ainsztein, J&J

Latif Alayour, Sensitech

Ronald Babinski, Baxter Healthcare

Narayan Balachandran, Amgen

Sud Barik, Wyeth

Kevin Beam, Seattle Genetices

Edward Beckles, Ortho McNeil Pharma

Ernest Bizjak, U.S. FDA

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Lyndall Brennan, AstraZeneca

Corey Brown, GlaxoSmithKline

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Kris Chatrathi, Burns & McDonnell

Jayesh Choksi, AumVis PharmaTec

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Wendell Yee, GTC Biotherapeutics

Kam Yong, Ngee Ann Polytechnic

Justin Zajc

Regulators to Speak at Pre-Annual Meeting Workshop

Las Vegas, Nev. • April 19 • www.pda.org/annual2009

Workshop Chair Stefan Köhler, AstraZeneca

On behalf of the Program Planning Committee and PDA, I would like to invite you and your staff to attend the PDA Workshop, *Cleanroom Technology and Contamination Control,* April 19, in Las Vegas. We believe that this workshop is something that you don't want to miss. The workshop will be held the day before the PDA Annual Meeting starts and at the same hotel. Join this event and get the most value from your trip to Las Vegas.

We have gathered expertise from regulatory authorities, industry and universities in order to make this workshop to a success. Our theme this year is *Cleanroom Technology and Contamination Control.* This theme is a multi-science discipline and requires various expertise. This is the reason why we have addressed our efforts to involve industry leading expertise into the workshop. Working with this theme, inspectors from the EMEA and U.S. FDA will give their views on current industry challenges, as well as a regulatory update in the opening session. All sessions will be followed by a question and answer session which we encourage everyone to take part and actively share knowledge.

Come and join this workshop to get the latest news on cGMP and have your questions answered.

We have also been able to obtain some of the most recognized persons in their working field which will provide for us the trends and cGMP within validation, risk management, airborne contamination, designs strategies and so forth. The conference will also feature a review of the soon to be published technical report within Blow-Fill-Seal technology and include a report on the comments received during PDA's global review of the draft.

Come and join this workshop to get the latest news on cGMP and have your questions answered. This is a great opportunity to calibrate your own thoughts with the rest of the world and you will have plenty of time to network during the day we are only short of one puzzle bit—*you!*

Finally, take this chance and expand your horizons and network by attending this highly scientific workshop designed for interaction between all attendances. It is my strong belief as a Chair of this event, that it is the event of the year in the field of clean room technology and contamination control. We look forward to seeing you in Las Vegas.

2009 PDA Annual Meeting

Futurist and U.S. FDA Computer Experts to Open Annual Meeting

At the *2009 PDA Annual Meeting* on April 20, **Ian Morrison** will give the keynote presentation. He is an internationally known author, consultant and futurist specializing in long-term forecasting and planning with a particular emphasis on healthcare. He has written, lectured and consulted on a wide variety of healthcare topics for government, industry and nonprofit organizations. Morrison is the author of *Healthcare in the New Millennium: Vision, Values and Leadership* and a co-author of *Looking Ahead at American Healthcare.* He is a founding partner of Strategic Health Perspectives, an ongoing forecasting service for clients in the healthcare industry.

Following his presentation, U.S. FDA's **J. David Doleski** and **Nicole Trudel** will co-present on *Computer Systems Applications within a cGMP Environment*, during the opening plenary.

Doleski has worked for FDA for 19 years. Currently, he serves as a team leader in CBER's Division of Manufacturing and Product Quality. For more than seven years, he has reviewed Chemistry, Manufacturing and Controls sections of biologics license applications and supplements. To date, he has performed 15 pre-approval and pre-license inspections. Doleski has participated in various policy groups, including FDA's Part 11 Committee. He was awarded CBER's Mentoring Award in 2008.

Trudel currently works for FDA as a reviewer in CBER's Division of Manufacturing and Product Quality. Her duties include reviewing Chemistry, Manufacturing and Controls information in biologics license applications and supplements; conducting pre-approval and pre-license inspections for biologics; and participating in various policy groups addressing cGMP, harmonization and inspection related issues for biologics. She is an active participant in the Global Harmonization Task Force (GHTF), and is the CBER representative to GHTF Study Group 3 for Quality Systems. Trudel also has industry experience in the bio-defense arena, and was previously the Chief, Test and Evaluation at the Joint Program Executive Office for Chemical and Biological Defense.

For 2009 Resolve to Give Yourself a Gift, Take a TRI Training Class

Las Vegas • April 23–24 • www.pda.org/annual2009

Stephanie Ko, PDA

If you haven't thought of a New Year's resolution yet, it's still not too late! Consider one that's attainable and gives an immediate sense of achievement—*take a class!* You're probably still recovering from a holiday season of giving, now give yourself the gift of improved knowledge, performance and value to your company. It's not hard to justify—it's training and a very worthwhile investment.

The Training & Research Institute (TRI) is returning to Las Vegas to offer a variety of training courses in conjunction with the *2009 PDA Annual Meeting*. This means that you get to benefit from a conference, a course, and a great location—all in one with minimal effort. The training courses will take place immediately following the conference from April 23–24.

Red Rock image used with permission

TRI training courses are being offered at the Red Rock immediately following the *2009 PDA Annual Meeting*

We're pleased to announce the creation of two new courses in response to the needs of our members and the bio/pharmaceutical industry. "Development and Implementation of Qualification and Validation Programs–A Risk and Science Based Approach," presented by **Harold Baseman,** COO, ValSource, is an advanced version of his other course, "Development of Qualification and Validation Protocols-A Risk Management Approach." The second new course, "Introduction to HACCP and Other Risk-Based Systems as Applied to Aseptic Pharmaceutical Manufacturing," is taught by **J. Kirby Farrington**, Research Scientist, Eli Lilly, and presents basic formalized methodologies such as HACCP principles and how they can be applied to pharmaceutical production.

Three previously offered courses have been expanded to allow more depth into existing content and more breadth on the topics to be covered. "Cleanroom Management," taught by **Anne Marie Dixon**, Managing Partner, Cleanroom Management Associates, will have added topics such as: site selection, updates on the ISO clean room standards and their applications, HVAC PQ outlines and requirements, environmental monitoring and smoke studies. **Frank Kohn,** PhD, President, FSK Associates, will be teaching, "Auditing for Microbiological Aspects of Pharmaceutical and Biopharmaceutical Manufacturing," and has expanded the level of instruction to a two-day course to include case studies of various microbiological contamination events found during audits. The third expanded course is "Risk Estimation in Aseptic Processing," presented by **Klaus Haberer,** PhD, Managing Director, Compliance Advice and Services in Microbiology, and the additional topics include CAPA as a tool to recognize and manage microbiological risks, training of personnel for aseptic processing, and development, validation and control of sterilization processes.

Finally, we offer three existing courses with previous successes based on topics of longstanding value within the industry. "Practical and Effective Application of Design Review as a Risk Management Tool," will be taught by **Miguel Montalvo,** President, Expert Validation. This course was newly offered last year and quickly sold out, so be sure to register as soon as possible. **Dan Gold**, President, D.H. Gold Associates, will be presenting, "Quality Programs–the Path to Continuous Improvement," and Eddie Ballance, Sr. Manager, Eisai, will be holding, "Media Fills for Aseptic Processing." While these courses have been taught before, our instructors continuously update and revise their presentations for improvement based on student evaluations and the ever-changing trends of the bio/pharmaceutical industry.

If any of our courses sound like a good match for your professional development–don't wait. These training courses are offered only *once* this year, so don't miss this opportunity…and the great food provided! The Training & Research Institute staff will be there to make your experience meaningful and will give considerable thought to your needs and recommendations for future courses. We really hope to see you there!

Learn About Current Endotoxin Practices in Paris

Paris, France • March 17–18 • www.pda.org/calendar

Conference Co-chairs Guy Roehrig, Eli Lilly; Gilles Goy, Charles River; Luc Pisarik, Merial

With great pleasure we wish to invite you all to the PDA Conference on Endotoxins that will be held in Paris on March 17–18.

The aim of the conference is to propose a review and an update on Endotoxins and Bacterial Endotoxin Testing from the now typical use of Limulus Amebocyte Lysate (LAL) testing for injectable forms to its potential applications to a broader range of products, the evolution of current testing methods and development of new techniques.

The conference will illustrate the current practices and the existing limitations and issues like sampling, preparation and non-compliance. Also depyrogenation techniques and GMP expectations will be presented and discussed.

During these two days, feedback from industry experts and lectures based on case studies will address problem solving, selection of appropriate methodology, routine monitoring options and comparison of values obtained.

The conference will cover all practical aspects on the topic and how limitations could be overcome. Finally, it will evaluate future trends and perspectives.

Round table discussions and posters are an opportunity for participants to share their practices, approaches and potential issues. They also will put you in the position to set requirements and acceptance criteria, as well as to join future workshops.

Your participation and contribution to the conference will be of absolute value. The conference is addressed to Scientists, Microbiologists, QC and QA, Formulation and Manufacturing professionals, Engineering and Validation specialists, Suppliers and Contactors.

Looking forward to meeting with you in Paris!

PDA's 3rd Workshop on Mycoplasmas Held in Berlin

Berlin, Germany • March 24–26 • www.pda.org/calendar

Barbara Potts, PhD, Genentech

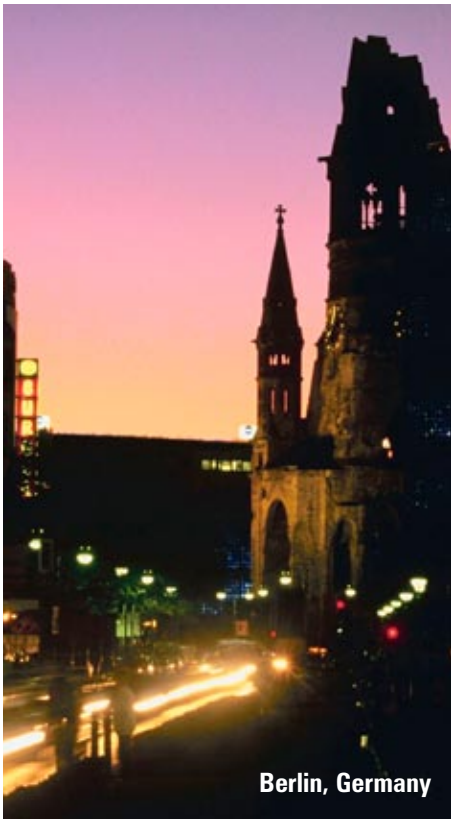
PDA is holding a third workshop on Mycoplasma contamination, with expanded sessions on Biology and NAT Assays. The previous two workshops covered hot topics and provided the foundation for future PDA TRs.

The first workshop was held in Washington D.C., in September 2005, in response to a rising incidence of mycoplasma contamination of media fills using plant and animal sourced media for both mammalian and bacterial expression systems. This appearance of mycoplasma in an unexpected stage in the biotechnology process came as a surprise to many.

The conventional wisdom had been that concerns for mycoplasma contamination were only during the mammalian cell culture fermentation stage and that plant sourced media were mycoplasma free. During this first workshop it became apparent that there were many other areas where the conventional wisdom about mycoplasma was challenged.

Vendors from the filtration and peptone industries openly discussed the pros and cons of filtration, heat, and testing and gamma irradiation for the control of mycoplasma. Many biotechnology companies freely shared their war stories about mycoplasma contaminations and the frustration that followed when trying to identify the source of the contamination. Data from rapid mycoplasma assays were also shared with the audience and some basic biology about mycoplasma was presented by **Len Hayflick,** PhD, Professor of Anatomy, University of California, the developer of the standard Hayflick media used for the isolation of mycoplasma and the discoverer of *Mycoplasma pneumoniae*.

A robust and productive discussion between the presenters and the audience revealed that the biotechnology industry had a problem and needed to share in the solutions. Proceedings from this first workshop that captured the discussions and presentations was published in 2007 (*Proceedings from the PDA Workshop on Mycoplasma Contamination by Plant Peptones*, Ed. **Barbara J. Potts.** Available at the PDA Bookstore). On the floor of this 2005 meeting, a PDA Mycoplasma Task Force was organized with many of the original speakers identified as leaders of the four task force subgroups. This Task Force is now 60 plus strong and is in the midst of developing three PDA technical reports and multiple publications on the standardization of filters for the removal of mycoplasma, the processing of plant and animal peptones and complex media for the removal of mycoplasma and a lengthy technical report on rapid alternate methods for the detection of mycoplasma.


Berlin, Germany

The second PDA Workshop, was held in Colorado Springs, Colo., in April of 2008, as part of the *2008 PDA Annual Meeting*. At this workshop the four subgroup leaders presented summaries of their work on their technical reports and additional biology presentations were added, including a presentation by **Robert Davis,** PhD, the discoverer of *Spiroplasmas*. A new session on the international regulatory requirements for a nucleic acid testing for mycoplasma and a session on industries experience with NAT assays acceptance with the EMEA and the FDA were added.

The 2009 Mycoplasma Workshop that will be held in Berlin from March 24–26 will build on the success of these two previous meetings. It promises to combine the robust and productive discussions from the first workshop and new information and data from the filtration, peptone and testing subgroups who have been hard at work putting the final touches to their respective technical reports. The *Biology of Mycoplasma* session has been expanded to add—in addition to Hayflick and Davis—additional world leaders in Phytomycoplasma (**Shmuel Razin,** PhD), and biofilms (**Hans-Curt Flemming**, PhD). The regulatory perspective on NAT assays for the detection of mycoplasma has been expanded to include to two FDA speakers one each from CBER and CDER, a former regulator from Japan (**Tsuguo Sasaki,** PhD), and a speaker each from the EDQM, the Paul-Ehrlich-Institut and the US Pharmacopeia. The industrial perspective on the international acceptance of NAT testing for mycoplasma will be presented by biotechnology companies who have submitted applications to the international regulatory authorities and will share with the audience their experience with these applications.

The round table discussion on the control of mycoplasma by the filter vendors and the peptone and media vendors will allow ample time for audience participation and for the vendors to share the pros and cons of various approaches. Vendors of commercially available mycoplasma testing kits will share with the audience their specific applications and supporting data at a breakfast and poster session. A mycoplasma survey using an audience response tool where immediate results are shared with the audience and a mycoplasma photo competition will round out this packed event.

PDA
Parenteral Drug Association

2009 PDA Pharmaceutical Cold Chain Management Conference

*From the First to the **LAST MILE**—Management of the Distribution of Temperature-Sensitive Pharmaceutical Products*

BETHESDA, MARYLAND
MARCH 23–26

www.pda.org/coldchain2009

CONFERENCE ○ March 23–24
EXHIBITION ○ March 23–24
TRAINING COURSE ○ March 25–26

Learn directly from industry, regulatory representatives, compendial experts, academicians and solution partners regarding the handling and distribution of temperature-sensitive pharmaceutical products. Presentations will address the following topics and provide you with the information you need to maintain product integrity and ensure patient safety throughout the product life cycle:

- Global Regulatory Environment
- End-user Perspective: The Patient
- "Last mile" for Clinical Trial Materials (CTMs)
- Good Cold Chain Distribution
- PDA Pharmaceutical Cold Chain Interest Group (PCCIG) updates
- Partners' solutions for the "last mile:" processes, equipment and materials

A two-day exhibition during the conference will feature companies with commercially-available technology and services for the handling of temperature-sensitive pharmaceuticals. Immediately following the conference, PDA's Training and Research Institute (PDA TRI) will offer a two-day course, *Global Regulations and Standards: Influences on Cold Chain Distribution, Packaging Testing and Transport Systems*.

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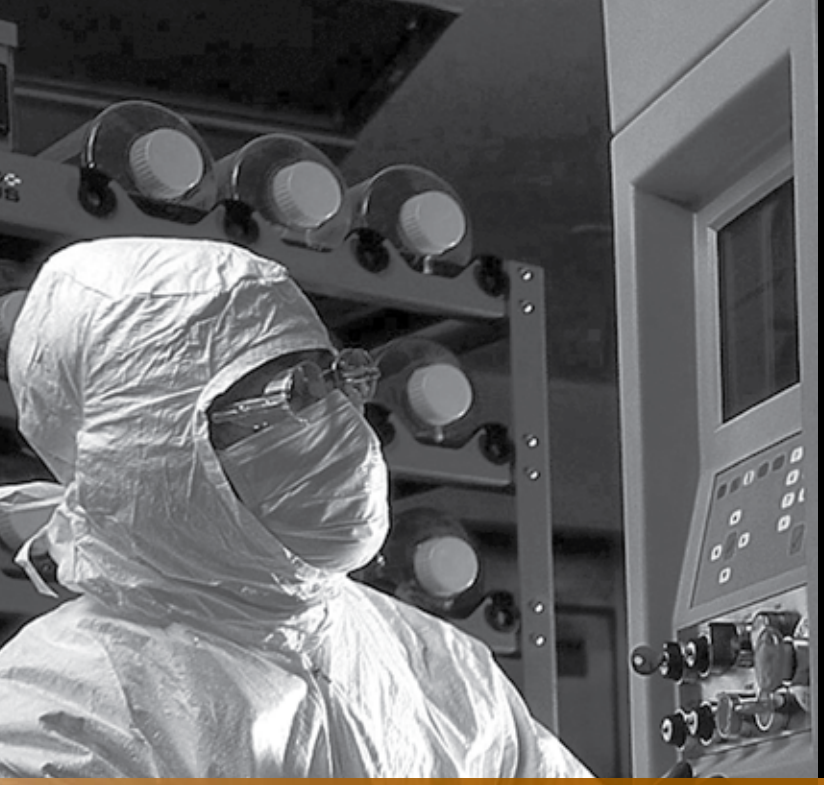

2009 PDA Annual Meeting

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

April 20-24, 2009

Las Vegas, Nevada

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

red rock
CASINO · RESORT · SPA
Las Vegas

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

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

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

Photos courtesy of Bayer Healthcare and Sartorius Stedim Biotech

www.pda.org/annual2009