

People

Science

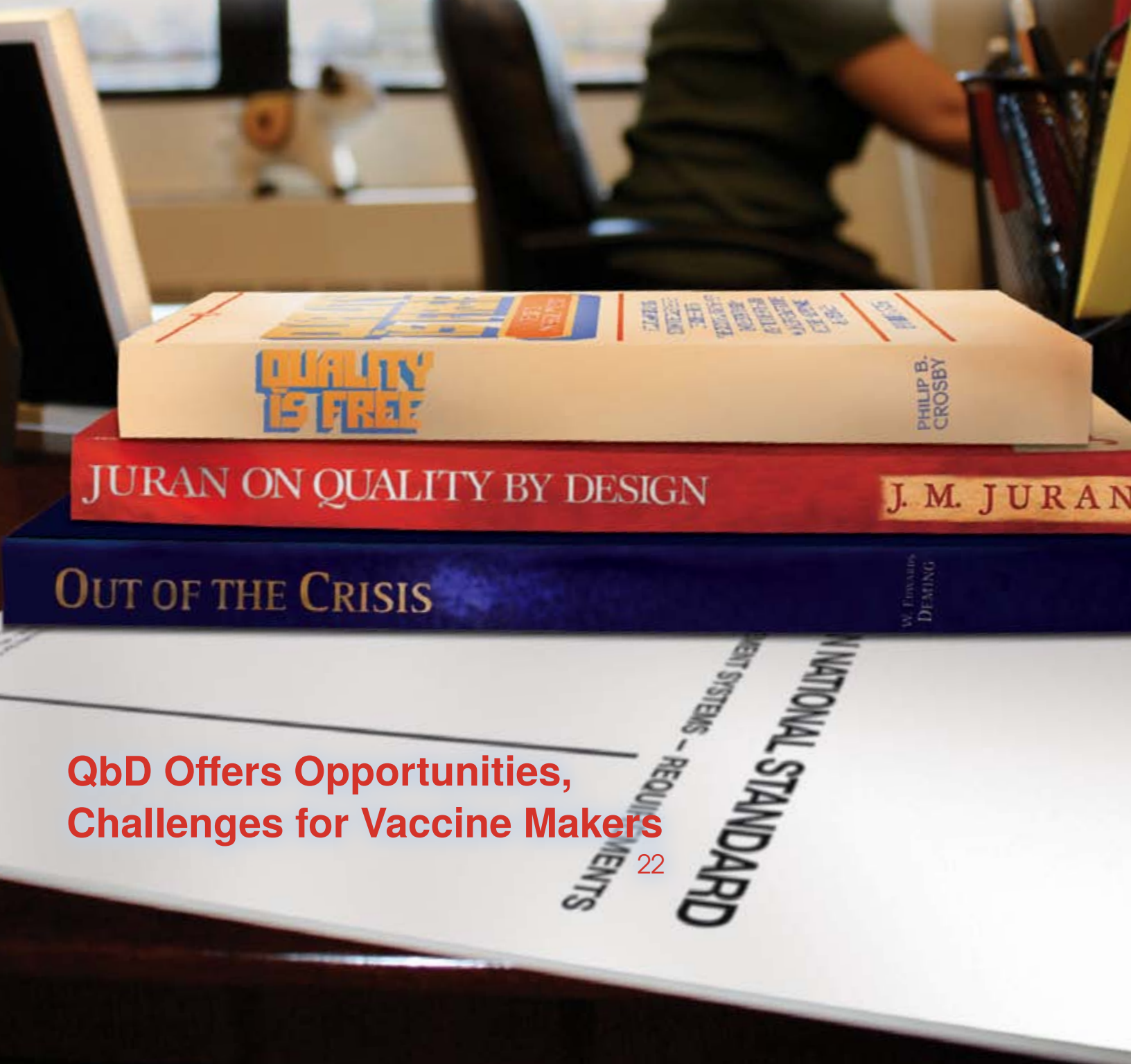
Regulation

PDA Letter

Volume XLVIII • Issue 10

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November/December 2012



QbD Offers Opportunities, Challenges for Vaccine Makers

22

26 Simplify Quality Systems, Experts Say

32 Make a Lasting Impression During PAI

34 Q10 Implementation Key for Executive Management

2013 PDA European Virus & TSE Safety Forum

4-6 June 2013 | Berlin | Germany



Call for Papers and Posters

On behalf of the Program Planning Committee and the Co-Chairs Hannelore Willkommen (RBS Consulting) & Kurt Brorson (FDA), we would like to invite you to submit a paper or poster abstract for presentation at the **2013 PDA European Virus & TSE Safety Forum** to be held in **Berlin, Germany on 4-6 June 2013**.

Paper abstracts and posters must be non-commercial in nature, describing new developments or work that significantly contributes to the body of knowledge relating to all aspects of Virus and TSE safety of medicinal products (biotech products, plasma products, ATMPs, vaccines).

Suggested topics include, but are not limited to:

- **Emerging Viruses of Concern**
(PARV 4, HEV, Heartland Virus)
- **Virus Safety of Starting and Raw Materials**
(PCV Inactivation & Removal Studies, Reduction by Chromatography, Traditional Virus Safety Testing and its Limitations, Modern Methods for Virus Detection)
- **Risk Mitigation**
(Root Cause Investigations, Preventive Actions)
- **Virus Clearance by Specific Unit Operations**
(Mechanism of Action, Robustness, Critical Process Parameters, Virus Carry-Over Studies, Impact of Virus Spike Quality)
- **TSE Clearance**
(Cell-based Assays, Prion Specific Filtration Methods, Scaled-down "Throughput" Studies)
- **TSE Risk Evaluation**
(Case Studies, Infectivity in Cell Substrates)

Case studies are particularly desired. Commercial abstracts for papers or posters will not be considered.

All submitted abstracts will be reviewed by the Program Planning Committee – submitters will be advised in writing of the status of their abstract after **31 January 2013**, or **17 May 2013**, respectively.

PDA Europe will provide one complimentary registration per podium presentation. Additional presenters and poster presenters are required to register for the conference at the prevailing registration fee. In addition, all presenters are responsible for their own travel and lodging. If you have any questions please do not hesitate to contact us.

Submissions received must include the following information:

- Title
- Presenter
- Presenter's biography (approx. 100 words)
- Additional authors
- Full mailing address
- Phone number
- Fax number
- E-mail address of the presenter
- Key objectives of your topic
- 2-3 paragraph abstract, summarizing your topic

Please send your abstract and the required information to Ailyn Kandora (PDA Europe) at kandora@pda.org.

Attention Exhibitors

PDA is seeking vendors who provide excellent products or services in support of the conference. Space is limited and is allocated on a first-come, first-served basis. To reserve your space, please contact Creixell Espilla-Gilart at espilla@pda.org or via telephone +49 (0) 33056 23 77 14.

Deadlines Abstracts of papers for presentation: 30 November 2012
Poster abstracts: 3 May 2013

The Parenteral Drug Association presents...



2013 PDA Europe Pharmaceutical Microbiology

*Product Quality Microbiology –
Keys for Successful Implementation*

A comprehensive program will include presentations from regulatory, industry and technology representatives from around the world.

Some of the highlights of the conference include:

- Rapid Microbiological Methods including validation of the methods
- Biofilms and water systems
- Environmental monitoring
- Contamination control
- Open panel discussion with regulators

Following the conference training courses covering Rapid Microbiological Methods, Biofilm and Contamination Control are offered.



Register by
4 Jan 2013
and SAVE!

26-27 February 2013
Hotel Marriott
Berlin | Germany



CONFERENCE 26-27 Feb | EXHIBITION 26-27 Feb | TRAINING COURSES 28 Sep-1 Mar

<https://europe.pda.org/Microbio2013>

Cover



Cover Art Illustrated by Katja Yount

22 QbD Offers Opportunities, Challenges for Vaccine Makers

Can both quality improvements and reductions in regulatory burden be realized by vaccine manufacturers who use the Quality by Design approach? Three FDA representatives shared their views on this very topic at PDA's *Applying QbD Principles in Vaccine Development* workshop in May to address this question and other questions regarding QbD and its viability to a cohort of manufacturers that has not readily adopted QbD.

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Are pharmaceutical quality systems too complex to be effective? According to an industry expert and a regulator, they are, and an injection of simplicity will help manufacturers improve quality performance.



32 **Make a Lasting Impression During Preapproval Inspection**

Everyone knows how important first impressions are. From a first date to a job interview, being prepared is always critical, and the lack of preparation can have lasting negative effects. This is especially true for preapproval/prelicensing inspections. Preparation for this event is key, even for companies with products already on the market, for the preapproval inspection is *the* moment to demonstrate to the regulatory authorities that your firm is able to produce a quality drug product.

PDA's MISSION

To develop scientifically sound, practical technical information and resources to advance science and regulation for the pharmaceutical and biopharmaceutical industry through the expertise of our global membership

PDA's VISION

To be the foremost global provider of science, technology, and regulatory information and education for the pharmaceutical and biopharmaceutical community



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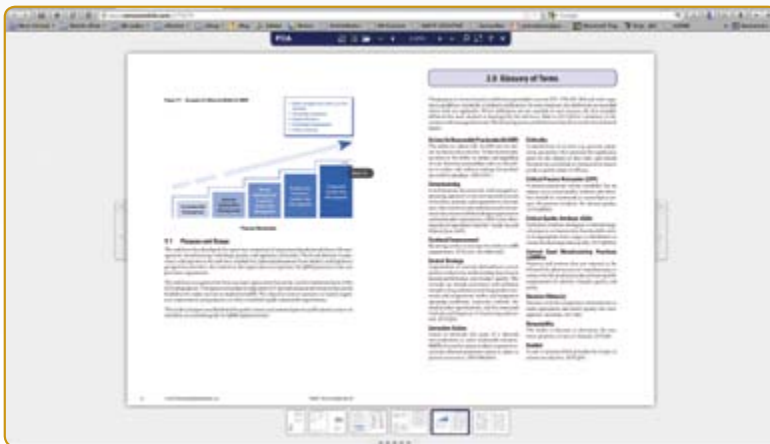
Glenn Wright,
Eli Lilly



Coming Soon

New PDA Member Benefit Soon to be Added

PDA MEMBERS ONLY: Welcome to Your Technical Report (TR) Portal



In this new portal, PDA members will be able to view the complete library (or collection) of PDA Technical Reports (TR).

The Technical Report Portal will be accessible to current Standard and Government members only and is for online viewing only. After logging on with your PDA ID number and password, you will be able to view the documents but cannot print, share or copy the documents. As a reminder, sharing your PDA ID number and password is not allowable under PDA's membership rules and may result in loss of privileges.

All print versions of the PDA Technical Reports are available for purchase at the PDA Bookstore.

PDA members are able to download electronic versions of newly released Technical Reports free of charge within 30 days of publication as a standard member benefit. Make sure PDA has your current email address to receive notifications when a new Technical Report is available for download.

PDA Technical Reports are highly valued membership benefits. They are global technical documents, prepared by member-driven Task Forces comprised of content experts, including scientists and engineers working in the pharmaceutical and biopharmaceutical industry, regulatory authorities and academia.

By the end of the year, PDA Members will be able to view all of PDA's Technical Reports for free!

www.pda.org/trarchive

PDA Europe is Hiring

PDA Europe is looking for a Senior Director to assist SR. VP Georg Roessling.

Position Description

The person in this position will be the deputy to the Head of PDA Europe. He/she will be in close exchange with the PDA membership, the PDA headquarters in the United States, and the Advisory Boards of PDA to identify the information needs of members. Activities according to PDA's strategic plan will include the development and organization of conferences, workshops, seminars and training courses.

Tasks

- Develop conferences and training courses
- Give presentations and present training courses
- Budget responsibility
- Personnel responsibility
- Travel

Education/Experience

- Background and degree in natural sciences (Biology, Pharmacy, Physics, Chemistry) or related experiences
- Minimum ten years experience in industry: Pharmaceutical or related industry with proven experiences
- Excellent knowledge of CMC and pharmaceutical processes
- General knowledge about pharmaceutical product development and manufacturing
- Distinguished service and history of contributions to PDA sponsored activities
- Excellent communication skills
- Knowledge of the relevant Microsoft tools
- Fluent in German and English

Location of office: Glienicke/Berlin, Germany

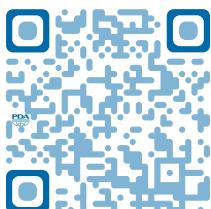
Position is open from January 1, 2013

Contact: Roessling@pda.org. 🌐



Have Impact on the PDA Letter

The PDA Letter Editorial Committee is looking for active PDA members to provide ideas for and comment on articles for the PDA Letter. For more information about this two-year volunteer commitment, please contact **Rebecca Stauffer** at stauffer@pda.org by December 1. 🌐



The Parenteral Drug Association presents...

2013 PDA Europe

Parenteral Drug Development

A good product development ensures less manufacturing problems and reliable product quality.

The topics at the meeting deal with:

- Workshop on VHP decontamination:
Risks to development and product stability
- Process issues
- Phase appropriate validation
- Future of clinical trial manufacturing
- Regulatory inspections of clinical manufacturing sites

Including
a Site Visit at
Boehringer
Ingelheim



Register by
14 Dec 2012
and SAVE!

11-13 February 2013

Maritim Hotel
Ulm | Germany



WORKSHOP | CONFERENCE | EXHIBITION

<https://europe.pda.org/ParDrug2013>



Volunteer

Lara Soltis, Texwipe, an ITW Company



Areas of Volunteerism: Chapter President, Chapter Secretary, Chapter President Elect

Your Job Title: Regional Sales Manager

PDA Join Date: 1998

Interesting fact about yourself: I started taking Karate this year and love it!

Why did you join PDA? I joined to keep abreast of hot regulatory topics in the industry (I was a QC Microbiologist)

Of your PDA volunteer experiences, which have you enjoyed the most? Seeing a meeting come together with help from only volunteers.

How has volunteering in PDA benefited you professionally? As a vendor now, it shows my customers that I care about what they care about, too.

Which PDA conference/training course is your favorite? The Microbiology Conference held in the fall. I'm still very interested in Microbiology, I guess you can take the girl out of the micro lab but you can't take the microbiologist out of the girl!

What would you say to somebody considering volunteering with PDA? Go for it! It's professionally and personally gratifying! You meet so many great individuals for networking, for friends and for professional advancement. 🍷

2011 Honor Awards Recipients

The PDA Honor Awards are bestowed on members who provide exceptional leadership and service to the Association, and have been awarded at the Annual Meeting since 1958. The 2011 award winners were announced at the *2012 Annual Meeting* in April, and they will be highlighted in each *PDA Letter* until next year's event. This month we highlight the Service Appreciation award.

The Service Appreciation Award

The Service Appreciation Award is presented annually for special acts, contributions or services that have contributed to the success and strength of PDA. The 2011 Service Appreciation Award recipients are:



Patricia Brown,
Agilent Technologies, Inc.



Myron Dittmer,
MFD & Associates



Jens Eilertsen, PhD,
Novo Nordisk A/S



Norbert Hentschel,
Boehringer Ingelheim Pharma



Maik Jornitz,
Sartorius Stedim Biotech



Stefano Macciò, PhD
CTP Tecnologie di Processo SpA



Peter Noverini,
BioVigilant Systems, Inc.



Amy Scott-Billman,
GlaxoSmithKline



Ano Xidias,
PharmOut Pty Ltd

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- Available in 8oz. spray can and 12"x12" individually packed wipes



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Faces & Places: 2012 PDA/FDA Joint Regulatory Conference

Welcoming Remarks



(l-r) Anders Vinther, PhD, Genentech; Richard Johnson, PDA

Quality Risk Management Implementation



(top l-r) Gregg Claycamp, FDA; Rick Friedman, FDA
(bottom l-r) Emma Ramnarine, Genentech; Markus-Peter Mueller, Swissmedic

Plenary Session



(l-r) Steven Mendivil, Amgen; Steven Solomon, FDA; Martin VanTrieste, Amgen

Plenary Session: Changing the Quality Culture



(l-r) G.K. Raju, PhD, Light Pharma; Anthony Mire-Sluis, Amgen; Greg Guyer, PhD, Merck Sharp & Dohme

Quality Systems



(l-r) Bob Rhoades, Quintiles Consulting; Ian Thrusell, WHO

Regulatory Considerations During Development of Biotechnology Products



(l-r) Jeffrey Baker, FDA; Patrick Swann, FDA

Cell Therapy Innovations



(l-r) Shane Killian, Johnson & Johnson; Kimberly Benton, FDA

Regulatory Submission and Meetings



(l-r) Angela Krueger, FDA; Mai Huynh, FDA; Richard Lostritto, FDA; Karen Long, Abbott Molecular; Nisha Jain, FDA

Plenary Session 3: CMO



(top l-r) Susan Schniepp, OSO BioPharmaceuticals Manufacturing; EJ Brandreth, PhD, Althea;
(bottom l-r) Christopher Masterson, SCubist Pharmaceuticals; Allan Coukell, Pew Charitable Trusts/ Pew Health Group

Manufacturing in the Future



(l-r) Thirunellai Venkateshwaran, Genentech; David Cummings, FDA; Vilayat Sayeed, FDA

Faces & Places: 2012 PDA/FDA Joint Regulatory Conference

Quality Agreements



(l-r) Paula Katz, FDA; Kenneth Drost, Amgen; Mahesh Ramanadham, FDA

International Compliance Update



(l-r) Carmelo Rosa, FDA; Robert McElwain, FDA

Emerging API Guidance



(l-r) Steven Mendivil, Amgen; Betsy Fritschel, Johnson & Johnson; Patrick Swann, FDA; Timothy Watson, PhD, Pfizer, Inc.

Foundation Session: User Fees



(top l-r) Catherine Cook, FDA; Carol Rehkopf, FDA
(bottom l-r) Theresa Mullin, FDA; Peter Beckerman, FDA

Excipient Best Practices



(l-r) Janeen Skutnik-Wilkinson, Pfizer, Inc.; Jeffrey Medwid, PhD, FDA

Foundation Session: Regulatory Process to Approval



(l-r) Laurie Norwood, FDA; Lisa Severy, Baxter Healthcare Company; Nicole Trudel, FDA; David Doleski, FDA; Valerie Flournoy, FDA; Mike Popek, FDA

Drug Safety



(top l-r) Steven Wolfgang, PhD, FDA; David Cummings, FDA;
(bottom) Lourdes Gonzales, Genentech, Inc.

Investigations



(l-r) Kris Evans, Amgen, Inc.; David Perkins, Abbott Laboratories; Renee Kyro, Abbott Laboratories

Plenary Session 4: Compliance Update



(l-r) Bob Dana, PDA; Steven Silverman, FDA; Armando Zamora, FDA; Mary Anne Malarkey, FDA; Martine Hartogensis, FDA; Douglas Stearn, FDA

Combination Products



(l-r) Donna French, PhD, Genentech, Inc.; Patricia Love, FDA

Plenary Session 5: Center Initiatives



(l-r) Steven Lynn, FDA; Rick Friedman, FDA; Amy Giertych, Baxter Healthcare Corporation; Martine Hartogensis, FDA; Howard Sklamberg, FDA; Christopher Joneckis, FDA

Faces & Places: 2012 PDA/FDA Joint Regulatory Conference

Concurrent Breakfast Sessions

Life Cycle Management



Brenda Uratani, FDA

Implementation Q8/Q11, Q9, Q10



Stephan Roenninger, PhD, F.
Hoffman-La Roche Ltd

Process Validation



(l-r) Hal Baseman, ValSource; Scott Bozzone, PhD, Pfizer, Inc.

USP



(l-r) Richard Friedman, FDA; Anthony DeStefano, PhD, USP; Jon Clark, FDA; V. Srinivasan, USP

Drug Shortages



Russell Wesdyk, FDA

Patient Advocacy



FDA Inspections



(l-r) David Doleski, FDA; Brooke Higgins, FDA; Colleen Hoyt, FDA

Passport Raffle



David Lino won an American Express giftcard from PDA



Klaus Madsen of Bavarian Nordic won the Amazon Kindle Fire from Commissioning Agents



Wendy Severs, of Shire, won a \$100 American Express gift card from Stelmi



Steven Laurenz of Abbott won an American Express giftcard from PDA



Kyla Neild, of Bayer Healthcare LLC, won an Amazon Kindle from Commissioning Agents



Brought to you by the PDA Career Center.
Go to www.pda.org/careers for the latest opportunities.

8 Reasons Why Opportunity Never Knocks On Your Door

By Vickie Milazzo

You feel like you do everything right. You work long hours. You're at the boss' beck and call. And yet, everyone around you seems to get richer and to gain more success, while you're stuck in the same old cubicle. Here's what needs to change in order for you to reach wicked success.

You're a hard worker. You stay late at the office and never complain. You're your boss' go to person on big projects. You're always taking on extra responsibility. And yet, your career trajectory is as flat as a board.

Meanwhile, you can't help but notice the coworkers who put in fewer hours than you but who've managed to get themselves promoted over you. Or that friend of yours whose long-shot cupcake bakery idea turned into a huge success. Or the countless wealthy businesspeople featured in the business magazines and blogs you read religiously who seem to have reached even greater success over the past few years despite the down economy. Of course, you're tired of merely scraping out an existence, but you've concluded real success is all about luck, and you just don't have any.

Wrong! If you want to achieve my brand of wicked success, it's all on you. Luck doesn't have anything to do with it.

I guarantee that the successful people you see every day don't have anything you don't have. There is no single factor that prevents success or one that guarantees

it. If you aren't driven by your passion or continuously working toward important goals, then of course, you're going to feel stuck in one place. But when you focus on your goals, plan your steps forward and have a little more faith in yourself, you *can* achieve wicked success.

The first step is to hold up a mirror and really examine what you're putting in at work.

Long hours don't always mean you're more productive than everyone else. If you are working longer hours and still getting nowhere, it is important to objectively assess the value of your output.

For example, how much time do you spend complaining? Do you have to discuss every issue ad infinitum no matter how small? Are you stealing time from the company to manage your personal life and counting it as work? Figure out how to become truly productive and to continuously make progress toward project goals. The success you seek will follow.

If you're still stumped as to why success has eluded you, read on as I explain a few success obstacles and how to get around them.

1 You Underprice Yourself

You'd love to ask for more money but frankly, you're afraid to. *The economy still isn't great so I'd better lie low,* you reason. This just seems like common sense. But settling for less than you're worth is a big mistake—even in the wake of the Great Recession.

In fact, if you're in the running for a new job or promotion, it might even cost you the opportunity. When I'm hiring, I actually weed out candidates who underprice themselves because I assume they won't perform at the level I expect. In my eyes and in the eyes of many other CEOs, job candidates actually lose credibility when they underprice themselves.

Many people mistakenly think they're doing their employers a favor by not pushing for more or that they'll be more appealing if they don't ask for what they're worth. The bad economy might be the current excuse, but I believe most underpricing occurs because many employees and job candidates just aren't comfortable asking for what they think they're worth.

2 You're Viewed As A Commodity

Commodities are easy to obtain and easy to replace. And that's certainly not how you want to be perceived at your job—whether you're an employee, a leader, or an entrepreneur. After all, if the people you're working with know that others share your skill set, they won't have any reason to pay you more or give you advanced opportunities. They'll be in control, not you. Do everything you can to ensure that you aren't seen as interchangeable or dispensable.

Do what you need to do to stand out. Get in the middle of everything and bring new ideas to the table. Build relationships throughout the company. If

you're able to make yourself invaluable and leverage the things that make you unique, you'll also make yourself impossible to replace. And when *that* happens, you'll be in control of your own price.

3 You Downplay Your Accomplishments

It can be hard to toot your own horn. But if you don't announce your own achievements, you can bet that no one else is going to do it for you. With humility, make sure that you're keeping your name, your accomplishments, and your skill set in front of everyone.

If you still have doubts, consider that announcing your accomplishments validates the investments others have made in you.

4 You Don't Network With Big Players

Generally, we tend to gravitate toward people who are similar to us: people who think similarly, who find similar things fun, and who are in similar walks of life. That's fine when it comes to your friendships, but you need to aim higher when it comes to networking. More than 60 percent of people find jobs through networking, for example, and you can bet that most of them didn't achieve this goal because they knew someone at the *bottom* of the pecking order.

No, I'm not advocating snobbery. It's normal to gravitate toward people who are the same as you—but in business, one of the main reasons people don't get ahead is that they don't get out of their groups. If you impress someone who is more successful than you are, they'll have a lot more influence than someone whose position is equivalent to yours.

5 You Doubt Your Abilities

It's highly unlikely that you'll reach any goal you set for yourself if you don't believe with your whole heart that achieving it is possible. Among other things, you won't be confident enough to take calculated risks if you don't believe that the limitations in front of you are surmountable. Anytime you find yourself entertaining doubts or trying to limit what you think is possible, remind yourself of your past successes. Let them infuse you with pride and bolster your resolve.

When I walked into my first meeting with a potential client, my legs were literally shaking. I forced myself to remember that this attorney needed specialized knowledge that only I—a critical care nurse—could give him. That reminder didn't banish all of my nervousness, but it did enable me to make the points I wanted. And I walked out of that meeting with my first client. I learned that when you expand what you're willing to believe about yourself, you can transform who you are and what your life looks like.

6 You Need A Mentor

There are two ways to develop the skills, habits, mindsets, etc. that you'll need to achieve wicked success. The first is to go it alone and learn by trial and error in the school of hard knocks. The second (much smarter) path is to learn from others who have encountered and surmounted problems that are similar to your own. That being the case, surround yourself with as many mentors as possible and practice the skills they pass on to you.

I've been in business for three decades, and I still learn every day from my students, staff, writers, speakers, business experts, and more. And in the early days of growing my business, I devoured every book on business strategy I could find, even though none were aimed precisely at the niche I was creating. Aggressive learning is a competitive advantage in achieving any desired goals.

7 You Are Too Bugged Down In The Little Things

In today's world, we're constantly sabotaged by nonproductive energy wasters. There are emails to read. Facebook statuses to update. Files to be organized. And on, and on. These are the easy, albeit often unproductive, tasks that make us feel good. They may not get you any closer to accomplishing your greater goals, but at least you've checked a couple of things off your to-do list.

Unfortunately, this addiction comes at a high price, because that cheap checkmark high is guaranteed to frustrate, overwhelm, and stress you out in the

long term. Breaking these addictions opens the door to achievement.

8 You Aren't Going After Your Big Goals

When is the last time you set a goal and really went after it? I encourage people to identify their "Big Things"—those goals that connect to their passionate vision. Then choose one to schedule their day around. For example, your Big Thing might be to get promoted. So today you might agree to take on a high-profile work project in order to put you in the running for that promotion. Set a target date for each of your Big Things. And begin working steadily toward achieving each of them. Start strong and you'll experience genuine elation from achieving real goals and solving real problems.

You can't snap your fingers and suddenly become successful. And the successful people you envy weren't able to do that either. They worked for it. Wicked success can be yours too if you make the same big commitments.

About the Author

Vickie Milazzo, RN, MSN, JD, is the author of the *New York Times* bestseller *Wicked Success Is Inside Every Woman* (Wiley, 2011, ISBN: 978-1-1181-0052-3, \$21.95, WickedSuccess.com). From a shotgun house in New Orleans to owner of a \$16-million business, Milazzo shares the innovative success strategies that earned her a place on the *Inc.* list of Top 10 Entrepreneurs and *Inc.* Top 5000 Fastest-Growing Companies in America.

Vickie is the owner of Vickie Milazzo Institute, an education company she founded in 1982. Vickie has been featured or profiled in numerous publications, including the *New York Times*, *Entrepreneur*, *Woman's Day*, *Success Magazine*, *Houston Chronicle*, *Ladies' Home Journal*, *Texas Bar Journal*, *Los Angeles Times*, *Philadelphia Inquirer*, and in more than 220 newspapers. Vickie has appeared on national radio and TV, including Fox & Friends and the National Public Radio program *This I Believe* and more than 200 national and local radio stations. 🚀

New Process Created for Technical Report Development

Richard Levy and Jahanvi (Janie) Miller, PDA

Over the years PDA's line of technical reports have gained popularity amongst members. Not only are these reports an important component in PDA's mission to "develop scientifically sound, practical technical information and resources to advance science and regulation for the pharmaceutical and biopharmaceutical industry through the expertise of our global membership" but they also represent the current best practices through expert authorship groups and a rigorous PDA peer review process.

Globally, PDA technical reports are recognized for applying sound scientific practice and current regulatory policy to daily operations in the production and quality control of medicines. Additionally, these reports offer an important contribution to the scientific literature and provide an enduring resource for best practices in pharmaceutical and biopharmaceutical technology.

In recognition of the importance of our technical reports, PDA announces changes to enhance the development process. These changes will hopefully ensure that members will continue to have access to thoroughly-investigated and documented reports serving as an up-to-date industry resource.

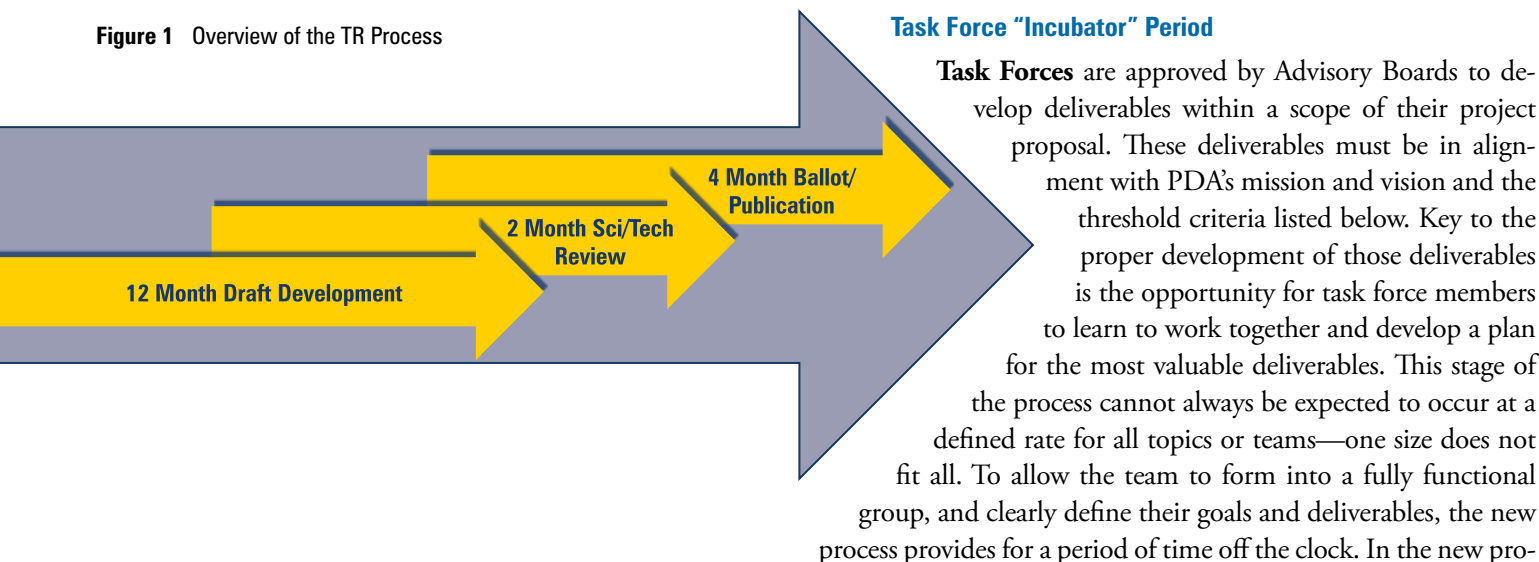
Why a New Process?

PDA recognizes that the time it takes to complete a typical technical report has been very lengthy. The traditional process has made it difficult for the member volunteers to stay engaged in the document development process. Since technical reports are often written to fill critical knowledge gaps in the practice of pharmaceutical technology or the interpretation of regulatory guidance, a second priority of the technical report process is speed to publication.

After listening to member feedback and careful analysis of our areas for improvement, PDA has developed a new technical report development process that should be more time efficient and easier to understand for members. Our aim is to improve the timeliness of these documents by adhering to this process. The new technical report process is a series of specific steps with defined timeframes and identified responsible parties intended to allow clear and coordinated teamwork.

Historically, it has taken more than three years to complete a technical report. A revised process for drafting technical reports has been developed which aims to reduce the time from inception to publishing to 18 months. This will be accomplished by defining roles and responsibilities, applying time frames to the steps involved, and providing guidance on best practices for producing quality technical reports. **Figure 1** is an overview of the new process.

Figure 1 Overview of the TR Process



process, rather than entering the technical report development phase, task forces exist in an "incubator" phase where task force members meet to determine their deliverables (which may include surveys, conferences, presentations, articles in the *PDA Letter* and the *PDA Journal of Pharmaceutical Science and Technology*, etc.) prior to starting to develop a technical report (**Figure 2**).

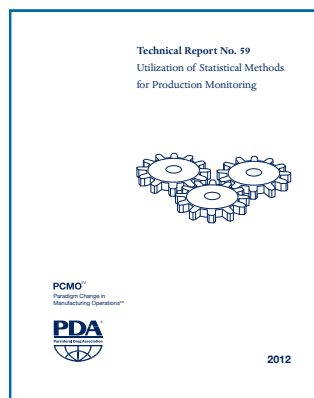
Task Force Formation: Threshold Criteria

Once it has been determined that a technical report is one of or the only team deliverable, the team must request to move into the **Technical Report Team** phase. In the past, most task forces moved directly into the report writing phase without achieving certain milestones which are

Continued on page 20

Technical Report *Watch*

PDA's Latest Technical Report Demystifies Statistical Methods




The pharmaceutical industry has seen increasing recognition in the role of statistical methods. As manufacturers seek to consistently produce products that conform to predetermined quality characteristics, statistical methods have historically shown their value in providing objective evidence in meeting this goal. Statistics are also

fundamental for the process understanding that is requisite for process improvement and development.

Industry and regulatory bodies like the International Committee for Harmonization, the International Standards Organization and the European Union have provided guidance on the use of statistical methods.

To help facilitate this process, PDA's Utilization of Statistical Methods for Production and Business Processes Task Force has produced a technical report that provides guidance in identifying and using statistical methods. The primary objective of this task force was to convey the appropriate use of statistical methods at a level most can understand.

The purpose of *Technical Report No. 59, Utilization of Statistical Methods for Production Monitoring* is to present relevant and easy to use Statistical Process Control Methods that are applicable to our industry. Advanced Statistical Methods such as multivariate models and Design of Experiments are covered.

The Technical Report is the latest produced as part of PDA's Paradigm Change in Manufacturing OperationsSM initiative. 



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Journal *Preview*

Final Journal of Year Looks at Quality

The PDA Journal of Pharmaceutical Science and Technology ends 2012 with two Commentaries on quality and a Case Study on quality risk management. Editor **Govind Rao** says it is time to revisit the idea of "open innovation," asking if there is a middle path between proprietary molecules and sharing resources in manufacturing and processing molecules, particularly biologics.

Editorial

Govind Rao, "Open Innovation"

Commentary

H. Gregg Claycamp, et al., "The Reliability-Quality Relationship for Quality Systems and Quality Risk Management"

Anders Vinther, Jennifer Magnani, "Can Quality Solve the Equation?"

Case Studies

Joseph Chen, et al., "A Novel Bacterial Contamination in Cell Culture Production—*Leptospira licerasiae*"

Tim Sandle, "Application of Quality Risk Management To Set Viable Environmental Monitoring Frequencies in Biotechnology Processing and Support Areas"

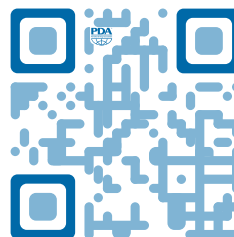
Research

Christoph Herwig, et al., "Information Processing: Rate-Based Investigation of Cell Physiological Changes along Design Space Development "

Technology/Application


David Meriage, et al., "Routine Screening for the Presence of Adulteration in Raw Materials Using Automated Nuclear Magnetic Resonance Spectroscopy"

Felipe Rebello Lourenço, et al., "How pH, Temperature, and Time of Incubation Affect False-Positive Responses and Uncertainty of the LAL Gel-Clot Test "



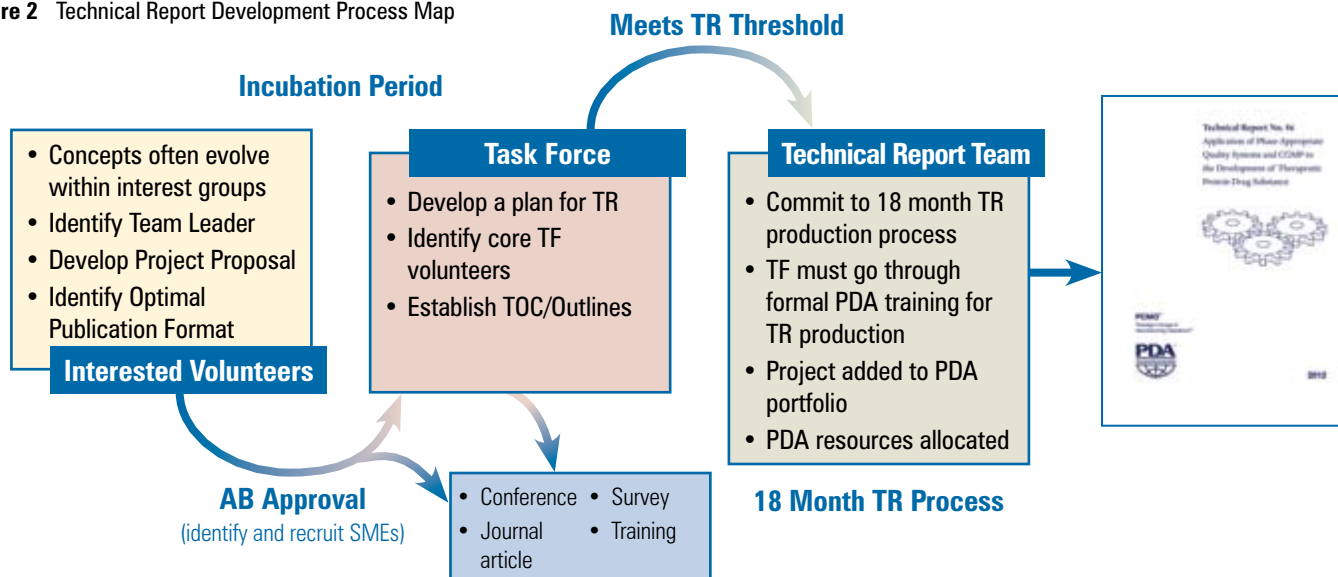
You can view the Journal at <http://journal.pda.org/>

Conference Report

Arifa S. Khan, et al., "Conference Report: PDA/FDA Adventitious Agents and Novel Cell Substrates: Emerging Technologies and New Challenges" 

New Process Created for Technical Report Development continued from page 18

Figure 2 Technical Report Development Process Map



critical for efficient development of reports. In the new process, a task force must meet the following criteria before progressing into the writing stage:

- There is a project plan and clear definition of the proposed technical report
- The technical report team reaches critical mass
- The technical report team agrees to PDA timeline and completion of training
- Volunteer agreement forms have been completed and signed

As an example, threshold criteria for a task force may include the following:

- 10-15 identified volunteers with requisite qualifications
- Committed and accessible leader and backup leader
- Understanding and commitment to a plan for completion of a technical report working draft in 12 months
- Commitment to completing process training at kickoff
- Agreements among task force members to technical report volunteer confidentiality terms and use of PDA publication tools
- Responsible party assigned for each stage
- Time frame applied for each stage
- Defined process milestones

The TR Development Process Map

The technical report process map (Fig-

ure 2) provides a high level template for technical report development. To achieve the goal of a timely publication, the map establishes an 18-month timeline and highlights major milestones for the technical report team, as well as outlining the progression and assignment of critical technical report team supporting activities, such as peer and Advisory Board review.

Scientific/Technical Peer Review

The first priority of the technical report process is to ensure the focus and quality of the end product. PDA technical reports are important and widely used reference documents for pharmaceutical professionals in industry, regulatory agencies and academia. Collective team expertise and a formal peer review by fellow industry experts ensure technical report quality. Once a technical report team has developed a working draft of their technical report, selected subject matter experts and PDA Advisory Board members are invited to participate in a peer review process. Peer review requires adherence to strict timelines to ensure that comments are prepared, reviewed and approved in a timely manner to meet specified deadlines.

Publication

Before a technical report is published it must be approved by a majority vote of

the appropriate Advisory Board and the PDA Board of Directors. Subsequent to resolving any Board issues, the document moves on to PDA’s Publication department. In addition to copy editing, PDA’s designer transforms the word document into the publication ready format.

New Tools

PDA has implemented some valuable tools to enhance the document accessibility and collaboration and to streamline the document review process. There are new resources in place, including an online PDA Workspace, technical report training modules and technical report handbooks for the Advisory Boards and the technical report teams.

Results

It’s too early to see the impact of the new process as existing teams begin to integrate into the new plan, and newly formed teams enter the incubation phase. The PDA leadership team (Board of Directors) is in full support of the re-engineered process. The Scientific and Regulatory Affairs staff is dedicated to continually improve on this initiative moving forward from the feedback of our members and volunteers.

We sincerely hope the new development process provides timelier access to relevant information for members of the pharmaceutical manufacturing community. 🌐

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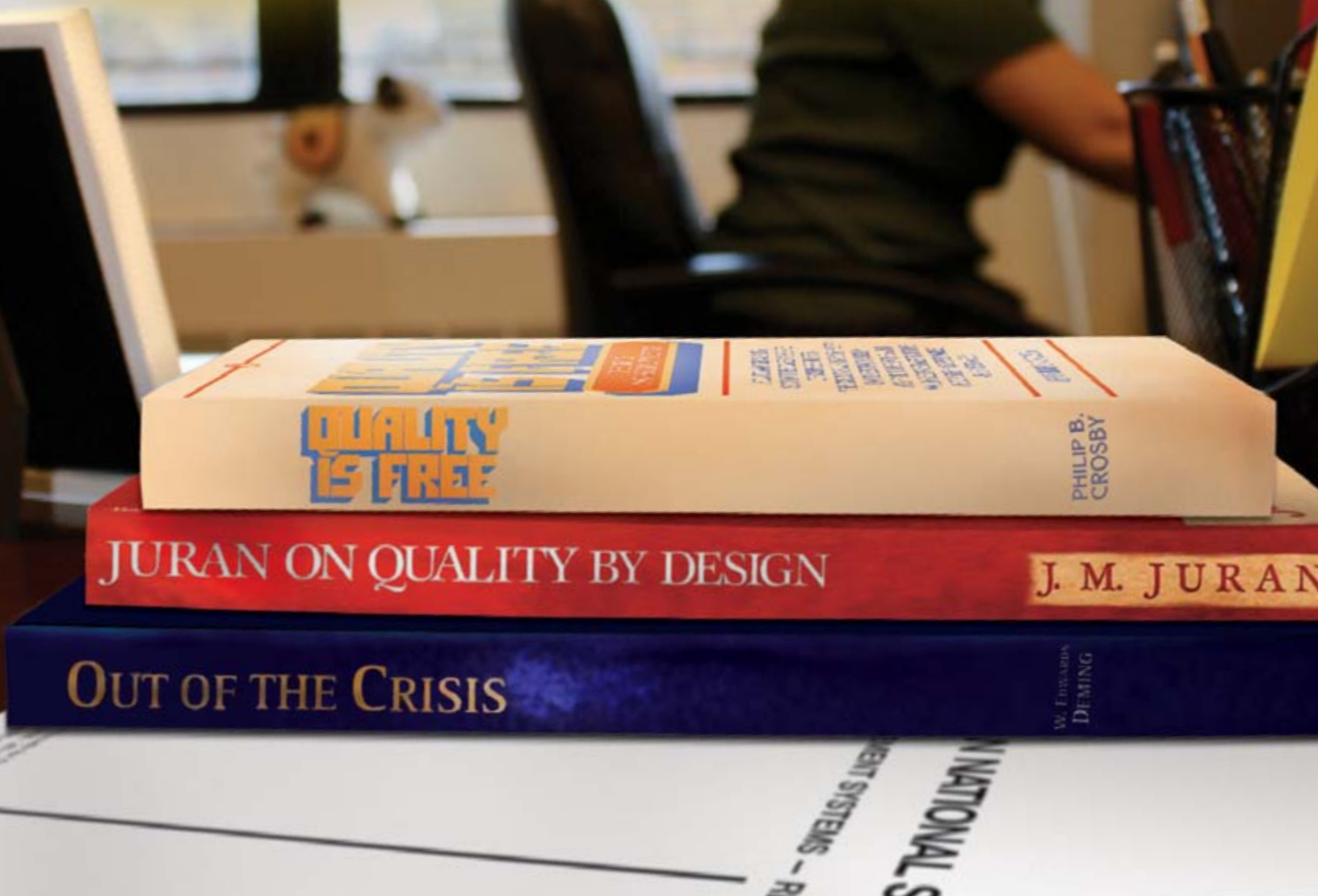
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QbD Offers Opportunities, Challenges for Vaccine Makers

Bob Darius, GlaxoSmithKline



Can both quality improvements and reductions in regulatory burden be realized by vaccine manufacturers who use the Quality by Design approach? Three FDA representatives shared their views on this very topic at PDA's *Applying QbD Principles in Vaccine Development* workshop in May to address this question and other questions regarding QbD and its viability to a cohort of manufacturers that has not readily adopted QbD.

While the FDA have not seen many QbD submissions with respect to vaccines submissions, the general consensus was that QbD may provide significant benefits for vaccine manufacturers.

Jay Eltermann, Director of Division of Manufacturing and Product Quality, CBER U.S. FDA, discussed the implications of QbD with regard to the lyophilisation process. At the beginning of his presentation he admitted, "I was a little bit surprised when I got the invitation [to present at the workshop] since Quality by Design is still somewhat new for our products and our product processes."

Although no submissions have been made using QbD for lyophilisation, Eltermann described lyo as a "good fit" for the use of QbD principles as equipment capabilities must be evaluated (such as shelf temperatures, heat transfer, vial types, and formulations), critical quality aspects and process parameters have to be defined, and risk assessments are used to make decisions. Addition-

ally, lyophilisation is a well-understood process that can be reliably reproduced. He provided illustrative examples of how QbD could be applied.

“I think when we look back at lyophilisation,” he said. “It equals one attempt to come up with a Quality by Design type of submission.” He further explained, “When you go through some of the examples where there were problems with the submissions, if they had followed [a QbD] approach—being proactive, being systematic...understanding the process control and having it based on sound science—you would have seen that many of the issues that we see during review and during inspection really would go away.”

Lyophilisation fits in well with QbD, he said, for the following reasons: **1)** It is a well understood, reproducible process; **2)** It uses accurate product testing that verifies process consistency; **3)** It features well-known and understood variables and controls (temperature, time, pressure, etc.); **4)** It involves precise process monitoring and process equipment control within narrowly defined limits; and **5)** It uses modeling of scale-up and process transfers.

Eltermann then discussed several points regarding what the design space for QbD of lyophilisation could be. Parameters to be defined include:

- product loading into freeze dryers and freezing rate
- control of primary and secondary drying (time, vacuum, shelf heating ramp rates, product temperatures, homogeneity of product temperatures)
- use of direct or surrogate measurements for process controls (moisture readings in condenser or chamber, near infra-red technology, etc.)
- vial types and effects on heat transfer
- lot sizes
- variability among different lyophilizers

He also provided an overview of recent lyophilisation issues noted during the review process. Inadequate product testing was one, often resulting from firms not conducting adequate sampling per shelf

or per unit. Also, tests not indicative of the long-term success of the cycle was another common testing failure.

The second issue involved inadequate equipment qualification, such as not knowing the equipment (not making sure the IQ and OQ is performed correctly, variability in temperature control, etc.).

Third, loading may not be well-defined and a loading pattern not determined/documented, which can affect aseptic processing. Fourth, inadequate validation of the loading cycle can be an issue. And finally, inadequate scale-up or technology transfer protocols.

Eltermann noted that all of these are big issues that come up during review, and a QbD approach could help mitigate these.

“Had they taken a more proactive approach [and] understood the process,” he said, “many of these issues would not come up during the review.” He encouraged attendees to engage in dialogue with FDA, particularly by conducting Type C meetings.

Recent CBER QbD Experiences Shared

At the same time, the Agency is starting to see more evidence of QbD applications with biological products. At times, a submission may be “ObD-like” and yet not identified as QbD. “I think we’re going to have to explore more and have more dialogue with the industry on how the QbD approach would take place,” Eltermann said.

As far as recent submissions of QbD-based applications, **Roman Drews**, PhD, Office of Blood Research and Review, CBER, shared recent experiences from actual reviews of QbD submissions for biological products. His office has mostly seen QbD applications for recombinant and plasma-derived products.

Drews provided an overview of some of the challenges with QbD implementation within the industry. Often the relationship between structural/functional properties is not well understood. Products never consist of a single moiety, and therefore, clinical safety and efficacy

can be impacted by factors other than a mechanism of action. Measurement of biological activity may not have a direct relationship to mechanisms of action. Changes in product structure and development often occur late in development with unclear understanding of significance to safety and efficacy. The interaction of all these factors also makes it difficult to demonstrate a link between process parameters and product performance at the time of submission.

“Last, but not least,” he added, “communication between the sponsor and FDA may be complicated because of the need to review a large amount of data.”

Like Eltermann, Drews encouraged early communication between companies and the Agency, including Type C meetings, to focus on how to implement QbD concepts before submission of either a biological license application or post-approval supplement.

Drews offered some insights on risk assessments. He told the audience that from FDA’s perspective, risk assessments may not always include all possible variables regarding composition of the starting materials (i.e., intermediates from preceding unit operations or raw materials). The importance of robust risk assessments which have been carefully challenged by cross-functional teams was stated as being a critical starting point in QbD.

In his experience working the submissions, he noted that analytical methods may not always adequately justify the proposed design space limits for the critical process parameters. Other times,

Article at a Glance

- Examples suggest lyophilisation processes would be a good fit for QbD
- Regulators urge early communication with the Agency on procedures for implementing QbD
- Risk assessments must be strong enough to withstand regulatory challenges

The inherent practice of continuous improvement could be perceived by some that QbD was not fully effective or accurate

additional empirical data were not provided to confirm the boundaries of the design space which were extrapolated by mathematical modeling. He has also seen that control strategies for other process parameters, such as noncritical process parameters, relevant to the performance of manufacturing steps were not outlined in the licensed application, nor were they supported by the process validation studies. Finally, justification of the scores used to assess risk for the manufacturing process steps and tested parameters should be documented by results of process validation and development studies and prior knowledge of process and product.

Philip Krause, MD, Acting Deputy Director, Office of Vaccine Research and Review, CBER, covered the regulatory side of QbD for vaccines, noting like other speakers that ICH (which covers QbD), does not explicitly apply to vaccines. However, he stated, FDA may choose to apply appropriate ICH documents to vaccine reviews.

Areas of QbD Application for Vaccines

He admitted that “QbD was originally developed with the intent to apply it to nonvaccine products. The key question...is whether there are principles of QbD that could be applied to vaccines.”

Because vaccines are given to healthy individuals, the tolerance for safety issues is low and changes in efficacy may not be immediately apparent for vaccine products, Krause said. Therefore, risk assessment tools may not capture the full range of potential risks, and risk assessments may be difficult to evaluate objectively. If risk assessments cannot withstand a challenge by regulators, the validity of the QbD approaches will obviously be challenged.

Krause outlined the following examples where QbD could be applicable to vaccine products: unit operations (lyophi-

lisation, etc.), platform products that share either important attributes or unit operations, and process information that can provide additional data on product quality.

Understanding the associations between clinical end points and process parameters are one of the challenges for using QbD in vaccine products that should be explored, he noted. Other challenges include performing carefully managed risk assessments that are balanced and ask the probing questions. There is also the possibility that risk assessment tools may not capture the full range of risks. Again, Krause stressed the importance of well-challenged risk assessments. Assay variability is another key area posing challenges to the use of QbD for vaccine production.

Another challenge specific to vaccines involves the design of appropriate quality systems through establishing an appropriate process control strategy, then integrating continuous improvement processes. New manufacturing challenges occur over time, and additional product knowledge is gained with more production experience. However, the inherent practice of continuous improvement could be perceived by some that QbD was not fully effective or accurate. Managing these potential perceptions, and a careful understanding and maintenance of a culture of continuous improvement, must be supported by both industry and regulators alike.

Krause said that the positive implications of using a QbD approach for vaccines include development of and support for specifications during the review and approval process. Improvements in process consistency over time would result in longer term benefits to manufacturers through reduced rejections and waste. The potential reductions which could be gained on regulatory filings or test-

ing, however, should not be the driver for implementing QbD, Krause warned.

FDA's QbD Expectations

Ultimately, FDA's overall expectations of QbD, as shared by the FDA speakers, are improved product and process understanding, resulting in improved process control and lower costs and losses. Additional expectations of QbD include: establishing well defined aspects that are critical to product quality, developing product and process understanding prospectively during product and process development phases, identifying variables that could impact product quality, safety and efficacy, ensuring consistent processes through enhanced process control and monitoring, and establishing more robust manufacturing processes by applying the knowledge gained.

The consensus among the speakers was that while QbD can improve the overall quality and reliability of products, real benefits in the reduction in regulatory requirements remain to be seen. All agreed that there needs to be further discussion on the topic between industry and regulators.

[Editor's Note: The upcoming February issue of the *PDA Letter* will center on QbD and we will publish the results of a survey concerning QbD and vaccine manufacturing. If you're interested in submitting an article, please email Rebecca Stauffer at stauffer@pda.org.]

About the Author

Bob Darius is Vice President of the Regional Quality Unit for GlaxoSmith-Kline Vaccine's four manufacturing sites located in Germany and North America. Previously, he worked in the FDA's Center for Biologics Evaluation and Research for 15 years. After leaving FDA in 2005, he worked at Biologics Consulting Group, then started an independent consulting company, Radius Biotechnology, LLC.

Bob is a Microbiologist by training and attended George Mason and Johns Hopkins Universities. ☺



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Simplification Can Improve Quality Systems, Experts Say

Rebecca Stauffer, PDA

Are pharmaceutical quality systems too complex to be effective? According to an industry expert and a regulator, they are, and an injection of simplicity will help manufacturers improve quality performance.

Giving their respective takes on this idea were **Rob Rhoades**, VP, Quintiles, who represented industry, and **Ian Thrusell**, Head of Inspections, World Health Organization, representing regulators, both of whom spoke at the “Quality Systems” session of the *2012 PDA FDA Joint Regulatory Conference*. Despite representing opposite sides of the industry, both concurred that a quality system can be designed as user-friendly without sacrificing expectations for clear and direct information.

Drawing on his experience providing regulatory consulting for pharmaceutical and biotechnology companies, Rhoades discussed management’s responsibility to quality. He began by drawing from *Risky Business: Managing the Quality of America’s Medicines*, a book he wrote many years ago that remains pertinent.

“It probably has been awhile since I

picked it up and dusted it off,” he said, referring to the book. “The original was written in 2003—almost ten years ago. When I picked it up and started reading it again, probably the most startling feature is that it really all reads like I wrote it yesterday.

He added that this scared him as “an awful lot of it deals with kind of all the things that go bump in the night...because, frankly that’s a lot of the things that my team gets called in to deal with.” He went on to mention that around 80-90% of his team’s work deals with 483 warning letters, consent decrees, etc.

“This has really become a truly global issue,” he said.

He then went on to note that most problems begin gradually and often remain unnoticed until the problems get big enough.

“We didn’t get there in a day,” he said. “Nobody goes to work and says ‘Gee, what non-compliant, non-quality work can I do today?’”

Ultimately, this breeds complexity.

“We’ve allowed complexity to get in our

way,” he said. “This is one of the challenges that management has to deal with. Ultimately, we ask employees to sit down and read 80-90 page SOPs and then go follow it to the letter.” Unsurprisingly, he noted that when FDA inspectors encounter lengthy prose SOPs, these inspectors realize compliance remains on shaky ground.

“We really as responsible managers have to find ways to push simplicity,” he implored.

Decision-making is another area that often falls through.

“Trying to get clear decisions articulated and carried out and executed is a really tough thing,” he said. “You really have to have a mechanism for problem-solving.” He followed up by noting that having a clear decision-making path is important due to the dynamic nature of the industry. Often, issues will occur at one site that staff at another site remains unaware of.

“The single biggest missing skillset in our industry today is the ability to conduct a proper investigation—solve a problem, get to root cause, and then turn that into an effective corrective action or preventive action,” he said. “If you can teach your folks to do that [root cause analysis], I will be out of a job.”

He noted that most firms are not proactive enough to conduct this deep level of analysis and instead are merely reactive, focusing on merely completing paperwork.

Rhoades then discussed an epiphany that occurred on vacation in Ireland when he visited Newgrange, an ancient, massive passage tomb built in 3200 B.C. All the stones used to build this 5,000-year-old structure were quarried from a site 70 km away by canoe.

Pointing out that it took three to four generations for the structure to be completed, he mused that today “we have a hard time getting people to follow an SOP twice two days in a row.” ➤



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Every year on the winter solstice sunlight comes through a passage built into the tomb for 17 minutes. The rest of the time, the passage is in complete darkness. All of this was accomplished without computers and other modern technology, stressed Rhoades.

“The complexity of this design and the fact that it took multiple generations to put this thing together such that it’s perfect in doing what it’s doing says to me, ‘you know what, we can do this,’” Rhoades said.

“Somehow or another we can carve through all of the things, all of the problems that plague us on a day-to-day basis to get us to a point where we can create our own little Stonehenge, whether it’s in the drug industry, medical devices, or whoever else from biopharma might be represented here today,” he said.

Going back to the industry, he said that management’s role is to make sure compliance happens in a consistent manner. Not surprisingly this is a challenge due to the disparate nature of large companies with disparate groups of people scattered across various sites and even in foreign countries where language barriers can be an issue.

“That really is the embodiment of compliance,” Rhoades said. It is the “cornerstone of the quality system.”

Lack of consistency often leads to a perceived disconnect between management and the rest of the staff. Rhoades noted that he often visits facilities where workers on the shop floor feel disconnected from management. In many cases, it is not just a perception but a reality.

“It really is our responsibility to lead the organization,” he said. Leadership, he pointed out, is one of the key foundations of a good quality system.

He wrapped up his presentation by management’s requirements for a good quality system: simple and clear guidelines, paths for direct action and problem-solving, and, in general, being prepared for when things go wrong.

Thrusell then provided a regulator’s per-

spective on quality systems and compliance culture, which mirrored Rhoades’ talk to some extent. He honed in on what regulators are specifically looking for when they review a company’s quality system.

“Why are quality systems actually necessary,” Thrusell mused rhetorically. “Well, on the one hand quality systems are good for you, they allow you to make whatever you are making, or the process that you are running, they allow it to be more consistent.”

On the other hand, for the regulators, “the reason we’re there and why we want to see the quality systems you have working effectively is because we’re interested, first and foremost, in protecting public health.” He then highlighted that, as shown by the history of medi-

Looking at how companies react when things go wrong is a really, really good diagnostic tool

nal regulations, responses have been two to three steps behind the latest disaster, from a recall of 59 million metered dose inhalers in the late ‘90s that led to the deaths of 17 children to the heparin crisis in 2007.

“Those just seem to keep coming up like a bad penny,” he said. “Every five or six years it seems to happen again. And one really has to ask yourself of why the world isn’t learning about that sort of thing.”

Thrusell pointed out that the major recalls and contamination issues in pharma generally “come down to some underlying cultural issue in the companies.” He told about his involvement in a British facility that manufactured flu vaccines that were later recalled and how that particular facility had a significant history, some good and some bad.

“Underlying what went wrong was matters of corporate quality culture,” he said. “And some of these issues here have to do with culture.”

Often a corporate culture can be influ-

enced by cost-savings. In itself, this is not necessarily a bad thing, Thrusell indicated, citing efforts to reduce the prices of HIV medications in sub-Saharan Africa.

“Cost is very, very important,” he said. “But when in an organization it becomes everything and particularly when it becomes very short term...[when] organizations are not planning for a sustainable future that’s when it starts to be problematic.”

Referring back to Rhoades’ point about simplicity, Thrusell cited the example of an investigation he was involved in at a facility in Pakistan. Here, an excipient was mixed with an active during the formulation of a product that contained a massive overdose of Pyrimethamine. Patients who took the drug received a month’s treatment four times a day. This caused the deaths of over 120 patients.

“It was one of the simplest GMP mix-ups—a mix-up in a dispensary adding the wrong material. We talk a lot about quality systems, rather sophisticated systems, but when things go wrong and they still go wrong today, it’s sometimes the most basic things,” he said. “So one little message away from all this is yes, by all means, we need good quality systems and we need good investigations, but we also need to keep things simple.”

In fact, he noted that continuous improvement has been a hallmark of the industry. Yet, at the same time, while this is a normal human behavior it is often stifled thanks to complexity.

“When people don’t understand their processes, they’re very difficult to improve,” he said. “So, really understanding processes, how they work and keeping them as simple as possible, is absolutely key.”

He then discussed what regulators are looking for when they visit a facility. Ultimately, they’re looking for the company’s “degree of compliance.”

“We’re interested in the things you do well, the things that you do right, the things you excel in, not just the things

you don't do so well in," he emphasized. "The deeper things we are asking ourselves is can you be trusted, do we trust you, when we walk out the door will those good things that you showed us in the procedures and so on... will they continue to do that same standard of work?"

He then pointed out that an inspector, like himself, must often differentiate between what a company considers a GMP and what the regulatory agency believes is sound GMP, noting that WHO's GMP guidelines are often more prescriptive than in industry.

Along with a good quality system, Thrussell identified leadership as a core area than an inspector looks at because "without that commitment those powers around there trying to erode your controls will continue at pace. If there's not leadership at the top and belief at the bottom meeting then there's going to be problems sooner or later." In fact, ICH Q10 specifically mentions senior management's responsibility to ensuring quality systems.

As with Rhoades' presentation, Thrussell also keyed in on risk analysis, pointing out that risk is not a new concept; it's mentioned 90 times within 20 different documents in EU GMP legislation and guidances.

"What's perhaps new is the lifecycle approach," he said. "But the concepts are not new."

As to why inspectors look at a company's quality management systems, Thrussell said that it's quite simple.

"Looking at how companies react when things go wrong is a really, really good diagnostic tool."

So, why are companies still having issues as far as quality since quality systems are standard across the industry?

"Well, clearly the management practices have failed," said Thrussell. "Risk management has failed. Identification has failed." Often these boil down to lapses in communication or even failures to leverage existing knowledge bases.

He then highlighted the features of a good quality system. These include: sys-

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temic monitoring of process performance and product quality using QRM, CAPA methodologies that result in improvements not just data, change management, and management review of processes, product performance, and quality. In essence, he said that quality should be the lifeblood of a company, so that even if it is not spoken of continuously, it is still present within the company's culture.

On that last point, he referenced a colleague who told him that "the more times people talk about quality and inspection, the more I know it's missing. So, if nothing else, when facing your inspectors try and use other words and do walk the walk and walk the talk and show that you are doing things."

Do you really need an 80-page SOP?

Ultimately, an inspector wants to leave a site with the confidence that when something does go wrong, the company has procedures in place to deal with the situation effectively.

Richard Friedman, Associate Director of Risk Science, Intelligence and Prioritization at CDER, U.S. and moderator of the session, opened the Q&A portion with a query of his own for Rhoades and Thrusell: “How do you know you have a good quality system,” he asked the two.

Thrusell responded that it helps to have something tangible to measure. “You can also measure the absence of things,” he added, although he cautioned that the absence of defects could also mean that they are under-represented and present. He then pointed out that other industries do proactive surveys as to the quality of their products yet this is not typical of pharma. He also recommended following CAPA processes.

“If they have too few deviations they don’t have a good quality system,” he said he often tells companies, particularly in India since he is skeptical that few things could go wrong despite the high level of activity.

“Either they’re employing super-humans or robots” he said. “Or there is some underreporting.”

Rhoades added that he thinks one measure of effectiveness in the industry is how often bad events recur. He noted that some companies do after-action reviews when things do go wrong. Just recently, he worked with company that was forced to recall a significant batch of medications and analyzed what factors

led to the recall and developed suggestions for preventing the situation from repeating itself.

Another audience member asked how a company can balance simplification while expectations for explicit information.

“Well, don’t confuse simplicity with not having clarity,” responded Rhoades. “We have a complex business to run, there’s no question about it.” He noted that overcoming complexity is a significant challenge for larger companies employing massive amounts of staff and managing multiple facilities across several locations. The industry can’t get away from the need from the need for clear specifications and processes. Yet, the goal of simplicity, Rhoades emphasized, is to get away from the minutiae that clouds thinking and understanding.

“Do you really need an 80-page SOP,” he asked. “Do you really need 80 pages—79 of which are written by somebody who is in another department? Do you really have clear understanding of how those intricacies and inter-relationships between departments and how they have to work?”

The effectiveness of training was also brought up during the Q&A. Rhoades admitted that training is “always a tough nut to crack.” Yet it is often a key point that his investigations must address, such as operator errors due to lack of adequate training.

“In terms of effectiveness,” he said. “There are a myriad of solutions out there in terms of the mechanisms to try and test. It’s a sore spot. I think a lot of companies struggle with the resources that are required to really have an effective training system at every level.”

On the point of training, Friedman indicated that a way to evaluate the effectiveness of training would be to measure

compliance with SOPs. He told the audience that when he was doing inspections, he would often sit next to a manufacturing supervisor who was blatantly ignoring an SOP that he had just read.

Toward the close of the session, Thrusell discussed his involvement in shutting down the British facility involved in the infamous flu vaccine recall. He talked about how for the four years after the shut-down, inspections were conducted by both the FDA and the Medicines and Healthcare Products Regulatory Agency. The company ultimately implemented procedures to prevent a recurrence. This illustrates that even breakdowns in quality, no matter how disastrous, can provide a learning opportunity for an organization. In the end, bad quality has the potential to give birth to good quality.


“Sometimes,” Thrusell said. “Good things happen out of bad experiences.”

About the Experts

Bob Rhoades is Vice President, Quality & Compliance Consulting, at Quintiles. Bob has designed and implemented compliance improvement initiatives for major manufacturers in the United



States, Europe, India and China. Bob has worked in concert with client counsel on a variety of legal cases and was selected to advise in the contaminated heparin crisis in 2008.

Ian Thrusell is currently one of the UK MHRA GMP Inspectorate Expert Inspectors and a member of the UK’s GMP Inspectorate’s Strategic Group which amongst its roles represents the Agency’s GMP interests at an EU and international level. Ian has a wide experience of international guidance development and implementation. He is rapporteur for the current amendments to Chapter 1 and 2 of the EU Guide. 



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Make a Lasting Impression During Preapproval Inspection

Rebecca Stauffer, PDA

Everyone knows how important first impressions are. From a first date to a job interview, being prepared is always critical, and the lack of preparation can have lasting negative effects. This is especially true for preapproval/prelicensing inspections. Preparation for this event is key, even for companies with products already on the market, for the preapproval inspection is *the* moment to demonstrate to the regulatory authorities that your firm is able to produce a quality drug product.

At the 2012 PDA/FDA Joint Regulatory Conference, **Lisa Severy**, Sr. Quality Regulatory Compliance Manager at Baxter Healthcare Corporation, and **Nicole Trudel**, Quality Assurance Specialist at CBER, U.S. FDA addressed prelicensing and preapproval, providing both industry and regulatory perspectives for one of the foundation sessions.

Representing the industry, Severy recommended that manufacturers view regulatory authorities as customers in a sense and to offer adequate preparations prior to inspection, ensuring the facility is ready and GMP compliant. Agents will need to see the facility in operation, observing manufacturing processes along with documentation. Inspectors will also want to see that effective quality systems have been implemented—these inspectors do not want to be handed draft SOPs. Available information should be accurate. Any requests for information and documents should be handled efficiently so that the preapproval inspection concludes on schedule. Ultimately, inspectors do not want to see any gaps or surprises.

Planning for a successful preapproval inspection, she indicated, is best started simultaneous with the project's kick-off. There should also be at least one team member with a background in quality. As far as scheduling, the inspection is usually planned for two months after the FDA receives the submission, generally, two months before due date for the action. During this time, cross-functional teams will provide frequent monitoring of readiness. The project team must also be apprised of the latest GMP requirements and expectations and then use these guidelines in the development of a timeline and "Master Project Plan" to ensure GMP compliance. This document, however, does not replace other documents, such as Master Validation Plan.



Much like a first date, it's best to strive for a good first impression in anticipation of an inspection.

During submission, Severy emphasized keeping the reviewer in mind by drafting a clear scope, summarizing the data, and ensuring the data is sufficient enough to minimize requests for additional information. The submission document should also be kept on hand during the preapproval inspection.

Severy also recommended conducting mock inspections prior to inspection and including related documentation. For the inspection preparation plan, all the parties involved should have clearly defined roles, rooms should be designated for inspection and inspection support, systems should be designed to efficiently retrieve and provide accurate information for specific requests, subject matter experts should be identified and delineated along with contact information, and participants should be trained adequately for the upcoming inspection.

At the late stage, just prior to inspection, relevant documents should be collected and reviewed then staged for inspection. The SOP index should be prepared. Next, rooms should be equipped in anticipation. Protective garments in appropriate sizes should also be available.

Once the inspection is underway, Severy said that it's important to remain calm and focused.

Process requests as efficiently as possible, ensure scribe notes are well-written, and be responsive to regulators' requirements. Good communication is key, she explained. She referred back to her earlier points about having a customer-service mindset when it comes to preapproval inspectors.

Daily, there needs to also be "wrap up" meetings between the company's inspection team and regulators. At the end of the

day, she recommends conducting a second, internal meeting in order to gather information and ensure pending requests are fulfilled. Additionally, this meeting will explore what needs to be prepared for the next day. Information from this meeting will also be emailed to key participants as well as management.

After the inspectors have finished is the opportunity to address any issues that arose during the inspection. If a Form 483 or other observation was issued, this is the time to make an action plan. Assign an owner for each observation. Define the schedule for completion/approval per the Agency's requirements and the company's specific policies. Review the response to ensure it is comprehensive, addressing all concerns. And make certain that responses are submitted on time.

If a 483 has been issued, after sending in a response, use it as a learning tool. Evaluate the things that went well and analyze if anything could have been done better. Implement whatever improvements are needed to ensure the issue does not recur.

Ultimately, the keys to a successful preapproval inspection in-

It's also pertinent to provide a daily agenda during inspection

volve many steps on behalf of the manufacturer. Begin preparations early. Ensure that activities are GMP compliant. Make sure that all team members involved are professional and knowledgeable. Develop a documented plan and adhere to it, acting quickly if deviations occur. Keep organized and committed to the goals of the inspection. Always meet the regulatory agency's requirements, and provide effective and efficient communication throughout the inspection.

Trudel then offered a regulatory perspective regarding preapproval inspection readiness, noting that the Public Health Service Act and Title 21 Code of Federal Regulations among other regulations require Agency inspections. As far as which division performs the inspection, it depends upon the nature of the inspection. If it involves a biologics license application, then it will involve regulators with either CBER or CDER. The Office of Regulatory Affairs handles new drug application, investigational new animal drug and pre-market application inspections.

She agreed with Severy on the importance of providing adequate feedback with regulators, both during and following the inspection, as well as providing a timely response to a Form 483, that allows for feedback. This would occur mid-cycle (in general, a cycle lasts for 120-300 days).

It's also pertinent to provide a daily agenda during inspection, she said. Establish start and end times that fall within reasonable business hours, with the expectation that production processes might require an alternate schedule. This agenda should also list the production schedule, updated daily, and include a daily closeout as well as lunch and other breaks as needed.

To ensure readiness for the procedure, make sure all processes are validated, all conformance lots manufactured, and all production and testing procedures have been approved. Ensure that all personnel have been trained adequately and that all equipment, facility, and supporting systems are qualified.

Logistically, regulators like to see that travel considerations have been considered. It also helps if key personnel have been identified and a list of dress requirements and restrictions has been distributed. Additionally, give the regulators forewarning regarding any immunization requirements necessary to enter the facility. Make sure there is adequate administrative support, including necessary support systems for badging, escorts, and in/out processing.

As far as documents, ensure that any documents requested in advance are available upon arrival. These requests may include the following: batch records, lists of SOPs, validations, deviations, change controls, etc., the quality manual, monitoring data and copies of the submission.

The subject matter experts should also be made available to the inspectors. The SMEs should represent production personnel, supervisors, and operators responsible for quality assurance, quality control testing, process validation, equipment qualification, quality systems, and facility systems (water, HVAC, cleaning, warehousing, etc.). Make sure that any requests for additional documents and information generates a timely response. Provide access to any relevant databases. And ensure that a SME accompanies the documents. If the business is conducted in a different language (since the Food and Drug Administration Safety and Innovation Act, or FDASIA, allows for more frequent inspections of foreign facilities this is expected to become more common), ensure that translation services are available for both documentation and discussion.

Trudel then offered an overview of past inspection issues she's experienced. In the area of biologics, she's seen incomplete process validation, uncorrected process failures, unresolved media fill failures, lack of in-process controls, lack of data supporting in-process hold times, lack of quality oversight, incomplete manufacturing and laboratory investigations, unqualified critical components or suppliers, issues with systemic mold, inadequate lab controls, unresolved enforcement actions or deviations, insufficient development of controls, in-

Continued on page 45



ICH Q10 Implementation Key for Executive Management

A PDA/FDA workshop for operations and quality professionals

Jennifer Magnani, Genentech, and Anders Vinther, PhD, PDA, Genentech

In a cosponsored effort, PDA and the U.S. FDA held a workshop focused on management's accountability within a quality system. The workshop consisted of short presentations that provided participants with background information and practical knowledge/experience from both industry leaders and FDA representatives. Participants were very active in the Q&A panel sessions, asking for clarifications and for additional detail or examples.

In order to encourage the participants to engage in a dialog and share with each other their experiences, challenges and tangible real-life examples, the workshop had four breakout sessions on the following aspects of the quality system:

- Best examples of a quality system
- Bad examples of quality systems
- Metrics for driving the right behaviors
- Governance models that support a robust quality system

Due to the EU releasing the revised EudraLex Volume 4 Chapter 1-Pharmaceutical Quality System and the connection with this workshop's focus, an overview of the changes was also presented.

ICH Q10 Introduction

The workshop started out with a presentation from **Neil Wilkinson**, Senior Partner, NSF-DBA, who participated in the ICH Q10 Expert Working Group as EFPIA's representative. He provided an overview of how and why ICH Q10 was conceived and the factors that contributed to the development of it and the related ICH guidances Q8 and Q9. He pointed to three factors in particular: 1) Industry and regulators wanting to change the "blind compliance" mentality; 2) FDA's cGMPs for the 21st Century Initiative; and 3) The PricewaterhouseCoopers (PWC) 2001 *Survey of Pharmaceutical Manufacturing*. The 2001 PWC report stated that the industry had low process capability, leading to

low utilization, high scrap and rework, and a high Cost of Quality.

Wilkinson repeated the oft-quoted 2003 *Wall Street Journal* passage: "The Pharmaceutical Industry has a little secret: Even as it invents new drugs its manufacturing techniques lag far behind those of potato chip and laundry soap makers." Against this background, industry and regulatory experts alike were envisioning a desired state of efficient, agile and flexible manufacturing that produces high quality drugs without extensive regulatory oversight. It was obvious that utilizing W. E. Deming's Fundamentals of Quality would lead the industry to this desired state.

With ICH Q10 going into effect in 2008 one would expect that industry had adopted these principles by now. This is not necessarily the case, Wilkinson said, because of several factors: 1) The industry has a less than mature understanding of quality management; 2) The connection between manufacturing and supply is generally poor; 3) Quality professionals are not always valued or not seen as adding value; 4) The legal requirement for independence of the quality unit drives bad behavior; and 5) The quality unit is not viewed as a business imperative. Regarding this latter point, Wilkinson said industry needs to begin thinking about quality in true financial terms.

The Operations, Quality Partnership

A very visible way that management can demonstrate to the organization that they have a quality culture is if quality and operations groups have a true partnership. Speakers from Genentech shared how this partnership works at the world's largest biopharma company.

James Miller, Vice President, Biologics and **Anders Vinther**, PhD, Vice President, Quality Biologics discussed how they work together to align their vision, mission and goals for their organizations. To make the partnership work in

reality, quality is truly "owned by all." The starting point for breeding this attitude is the organizational structures. They need to be designed to push accountability and responsibility down to the lowest level within the corporation. Governance models need to align to the organizational structures. "Ingraining Quality" is a concept that Miller and Vinther described as systems plus processes plus capabilities plus mind-set. Once ingrained, a quality culture blossoms, which places the patient as the number one consideration when decisions are made.

Regulatory Expectations

FDA's **Steven Lynn**, Director, OMPQ, CDER and **Rick Friedman**, Associate Director, OMPQ, CDER, spoke about the Agency's expectations for a pharmaceutical quality system in general and for executive management in particular.

"A quality system doesn't just mean the quality unit," said Lynn. "In other words, it's the sum of the whole and it's made up of all the functions that are involved in the manufacturing of the drug—from the purchasing agent who orders the raw materials to the operations manager who sets the production schedule to the quality manager who checks the batch records." Ultimately, quality is owned by all, end-to-end of the supply chain.

Lynn specified concrete Agency expectations for executive management. They are:

- **Assuring a state of control:** Vigilantly oversee quality; detect new variables or events potentially impacting products; create a proactive quality culture; and support continual improvement,
- **Commitment to quality:** Develop high quality standards, rather than settling on perceived 'regulator's minimum standards;' Here, Lynn mentioned the *PDA Survey on Cost of Quality* (to publish soon) which showed a linkage between high costs of business when identifying and solving quality prob-

lems after the fact rather than pursuing truly effective preventive measures, and

- **Reinvest in process and quality improvements:** Here, Lynn said financial support from top management is key, as reinvestment in systems, processes and facilities and active reduction of complaints and investigations is needed.

Friedman focused on the current expectations for a quality system, including sound risk management, maintaining a state of control, and the importance of a quality culture that leads to sustainable compliance. He noted that evaluation of a firm's quality system is central to FDA's systems-based inspection program (7356.002).

Friedman noted opportunities to lower risks by implementing contemporary manufacturing systems (like process analytical technologies, automation, rapid access barriers and isolators, etc.) to improve outmoded or even deficient facilities and processes. Industry's general lack of understanding of the causes and effects of ingredient variability is an impediment to adequately managing such risks, he said. He also discussed current expectations regarding CAPA, technology transfer, change management, process control, and management review.

Regarding corporate leadership and quality culture, Friedman emphasized the old adage *actions speak louder than words*. FDA wants to see quality managers involved in business decisions that have direct and even indirect impact on drug quality. Friedman stated, "The quality of the work you accept becomes your standard." What is written in an SOP or company credo is not meaningful to staff if your daily actions are contrary to them. Employees notice when senior managers keep high quality standards and show commitment to reduce mistakes/deviations or prevent them from happening. It is the company's choice of either moving towards a strong corporate quality culture and manufacturing consistency or towards unreliable systems and manufacturing problems.

The quality of the work you accept becomes your standard

The latter ultimately causes quality issues and poses great risk to the company business and the supply of products to the patients.

On several occasions, Lynn cited CDER Director **Janet Woodcock's** commentary in the May-June 2012 *PDA Journal of Pharmaceutical Science and Technology*. One powerful passage he cited was:

"Clearly the responsibility for maintaining quality rests squarely with the manufacturers themselves...the widespread and successful adoption of six sigma and related quality management techniques in other manufacturing sectors would imply that reliable, high-quality manufacturing is also attainable in the pharmaceutical sector. We must ask ourselves, in an area where the stakes are so high, why is this not being achieved?"

Operational Excellence/Efficiency

One of the common themes throughout the workshop was how important it is for drug manufacturers to use Operational Excellence (OE) tools and approaches to continually improving quality systems and business processes.

Gerry Migliaccio, Migliaccio Consulting (formerly with Pfizer), who was the Industry Rapporteur for ICH Q10, said the expert working group believed that a robust pharmaceutical quality system starts with GMP and overlays the concepts of an ISO Management System and the principles of OE.

He relayed lessons learned during Pfizer's implementation of a Right First Time strategy that led to a high performing supply network enabled by OE. Objectives of the OE approach were effectiveness, efficiency, predictability and continuous improvement, and it included people at all levels in the organization. Key to the OE program's success was the ability to change the company's culture and structurally supporting it with thorough OE training of key subject matter

experts.

The challenges involved with establishing a proactive, process-oriented culture in a highly regulated environment was discussed by Migliaccio and other speakers throughout the workshop. The key question is: How do firms encourage continually improving operations to lessen variability and raise quality when regulatory submission procedures globally are tedious, costly and inconsistent from region to region? All speakers and audience participants agreed that everyone—patients, regulators, and companies—will ultimately benefit from companies focusing on process and product understanding and efficiency. Quality by Design (QbD) may be one approach to achieving this, but so far, success has been very limited in the industry. A big problem currently is that the time it takes to implement manufacturing changes may be measured in years rather than months.

Another theme at the workshop was how well quality systems and continual improvements using OE tools go together to improve both the quality of the products and reducing variability and waste in operations. Migliaccio mentioned that many quality improvements were easier 'to sell' (i.e., met with more excitement by upper management) when presented as OE projects rather than quality improvement plans.

The importance of OE was also stressed during **Martin VanTrieste's** (Senior Vice President, Quality, Amgen) presentation, "An Effective Quality Management System – Cost of Doing Business or Competitive Advantage." He opened with some classic Deming quality quotes, including, "A bad system will beat a good person every time," and "Improve quality, you automatically improve productivity."

VanTrieste said that if we moved our industry from Three Sigma operations to Six Sigma operations, we would save \$50 billion annually.

Q10 has moved expectations beyond GMP to that of continual improvement, risk management, knowledge management, lifecycle, and risk/science-based opportunities—all elements that make good business sense. When integrating the quality system into the general business processes, companies will start to see the value for the bottom line.

VanTrieste said that CAPA systems should help firms identify weaknesses to avoid issues, promote root cause analysis, and use relevant metrics and management reviews to monitor performance and drive continuous improvement.

Quality Culture

Health authorities are placing more and more emphasis on organizations and each individual department within an organization to have a healthy quality culture. But what does that mean? The bottom-line is that it can mean different things to different organizations and individuals.

Catalent Pharma Solutions' VP of Quality Operations Dr. **Swroop Sahota's** definition of a quality system is simple: "A set of interrelated processes that work together to assure product safety, strength, identify, purity and quality." All employees need to understand that all work is a process and to maintain compliance system ownership is a must.

Sahota says a company's quality system should not be a stagnate system; rather, it needs to be continuously improved and kept up-to-date on current regulations. Sahota suggested the use of OE methodologies and tools for identification and implementation of changes. One should consider the following elements when developing a quality system:

- Simple to understand
- Clear roles and responsibilities
- Establishes accountability

- Reflects the company's vision and values
- Promotes commitment

Having a strong quality culture can also help an organization break down the complexity that adds risk to the supply chain and ultimately the products. **Jennifer Grealy**, Vice President, Manufacturing and Supplier Quality Assessment, Pfizer, defines a quality culture as, "An environment in which each and every

All employees need to understand that all work is a process

person understands and embraces their responsibility for protecting product quality and patient safety." This culture should be created and nurtured by leadership because it is one of the most fundamental elements that enable an organization to deliver quality products.

Importance of Training

Jennifer Magnani, Associate Director of Quality, Genentech, discussed the importance of a quality education for all in the organization. Investing in people throughout the organization can have a very strong impact on your quality system. Ensuring that quality professionals are trained well for their job is essential but looking beyond that standard training is what can take an organization to the next level.

Training programs on quality should target the people that play a role in getting products to patients, not just quality professionals. It should also include the procurement, operations, regulatory and IT departments. Additionally, organizations should look at focused training courses to enable learning on topics such as investigations or regulations. Certification programs in various fields would help facilitate this kind of learning.

In conclusion, the Q10 Workshop showed

that FDA has very clear expectations to senior management in terms of assuring a state of control, commitment to quality and reinvesting in process and quality improvements. The quality system expectations should be an integral part of the quality culture of a company throughout the organization and at all levels.

The workshop also showed that pharma companies are still developing in this area and are actively working to have a truly shared responsibility of quality between quality unit and operations departments.

[Editor's Message:

Anders Vinther offers his personal perspective on the workshop in the first "Voices of the Board," on p. 52.]

About the Authors

Anders Vinther is responsible for the technical operations at all Roche and Genentech Biologics sites (ten sites in Europe, US, and Singapore), and for products produced at these sites. Previously, he led the Global Quality System and Processes organization. At PDA he is currently a member of the Board of Directors, Chair Elect, and Quality Systems Interest Group Leader. Most recently he chaired the PDA Strategic Plan.



Jennifer Magnani's areas of responsibility include management of global quality portfolios, strategic global quality projects, GMP document governance for all of Roche Pharma's technical operations, strategic communication, global quality training program and quality council governance. She is managing the integration of a global Roche Pharmaceutical Quality System (POS) program. At PDA, she is consulting the Board on the Strategic Plan development and implementation, as well as organizational governance. 




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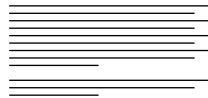
The following timeline represents expected milestones the U.S. FDA must meet concerning provisions of the Food and Drug Administration Safety and Innovation Act (FDASIA) over the next five years. 

'12

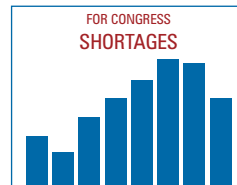
**July 19**

FDASIA signed into law

'13

Guidance for Industry**July 19**

Issue a guidance outlining the circumstances for denying or limiting required inspections

**December 31**

Submit to Congress a report on drug shortages and mitigating actions (report required annually thereafter)

'14

January 19

Issue a draft guidance on accelerated approval requirements for "breakthrough therapies" (final guidance required in one year)

**February 1**

Compile and submit inspection reports to Congress (and annually thereafter)

**July 19**

Drug importers must demonstrate the regulatory status of the drug, provide proof of facility registration with the FDA, and meet CGMP requirements, export regulations, etc.

'15

**July 19**

Commercial importers will have to register with the FDA and provide a unique identifier for associated establishments

'17

October 1

Manufacturers can take advantage of the Agency's ability to consider single enantiomer drugs as new chemical entities

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Interest Group *Corner*

New Interest Group Seeks Answers for Outsourced Operations Issues

Like many industries, pharmaceutical firms are outsourcing portions of their operations for greater cost-savings. Unlike other industries, the use of outsourcing partners can lead to significant regulatory hurdles. In fact, under 21 CFR 200.10(b), the U.S. FDA states that the Agency “regards extramural facilities as an extension of the manufacturer’s own facility.” Foreign regulatory bodies are also scrutinizing outsourcing relationships within the industry.

On Sept. 11, the Outsourced Operations Interest Group met for the first time at the *2012 PDA FDA Joint Regulatory Conference*. This meeting could not have been timelier; that same week, Chapter 7 of the European Union GMPs was finalized with the title “Outsourced Operations.” Headed by co-chairs **Karen Ginsbury**, President of PCI Pharmaceutical Consulting Israel Ltd., and **Susan Schniepp**, Vice President, Quality and Regulatory Affairs for Allergy Laboratories, the group identified many perceived problems with outsourced manufacturing operations which the interest group intends to address. Two topics that came up repeatedly were communication issues and lack of information flow between parties.

The *PDA Letter* spoke with both Ginsbury and Schniepp about the new interest group and the next steps the group will take in the coming months to address these issues.

While a supply chain interest group already exists, Ginsbury said that she and Schniepp felt “there was a need for both” as “supply chain is big and tends to focus on starting materials and the other end (distribution), tampering and counterfeit medicines.”

She also noted that “Outsourcing is just that—i.e. the increased use of CMOs, outsourced toxicology studies, outsourced validation, calibration activities, outsourced computing / IT—and the list is growing all the time. There are major issues experienced by both the Contract Giver (sponsor) and the Contract Acceptor (contractor) and we thought PDA should have a forum to hone in on those topics.”

“We’re very interested in what’s facing the contract organization,” agreed Schniepp who will be speaking on behalf of contract manufacturing organizations at the upcoming supply chain conference. As far as supply chain issues that affect and interface with outsourced ops, she cited instances of companies restricting where contract organizations can procure excipients.

She expects supply chain issues to become a major topic in the area of outsourced manufacturing.

“I do think it’s a topic that’s starting to emerge,” she said. “Because more and more companies are going to start putting in their quality agreements issues like where you need to get approval from us before you buy from this company or there needs to be an audit on hand. So I think it’s going to be a good element to start adding in.”

As far as the biggest issues in outsourced operations the group is facing, Ginsbury said that off the top of her head these included technical agreements and quality contracts that are too long and cumbersome. Companies often mistakenly believe the contract is a replacement for risk management tools. In addition: engineering batches and validation; an over - emphasis on customer audits of the service provider yet none of the Contract Giver’s (quality systems).

Of the latter, she and Schniepp noted at the interest group meeting that contractors are constantly being audited—at the initiation of the contract, for the annual GMP inspection, required regulatory audits, etc. Their presentation noted that for CMOs, almost half the year consists of audits!

Schniepp also highlighted the complex nature of outsourced manufacturing. Despite her 33 years of industry experience—including five in contract manufacturing—she noted “I thought I knew everything before I went into contract manufacturing but I found out I knew very little. It’s very complicated. I think the entire industry has to wrestle with the fact that big companies aren’t going to build big facilities anymore and what they’re going to do is rely on contract organizations to produce the product.

“And I think the most active area is certainly anything done aseptically by a contract manufacturer because those facilities are very hard and costly to maintain. You have to maintain them even when you’re not running product,” she added.

With regard to the recently enacted Food and Drug Administration Safety and Innovation Act (FDASIA) law, Schniepp said “I think that it [FDASIA] will affect it [contract manufacturing] because it will definitely raise the standard for everybody.”

Ginsbury also added that outside of FDAISA “there is ever increasing scrutiny—rightly so—of outsourced operations.”

At this time, Ginsbury and Schniepp are preparing the interest group for the upcoming Annual Meeting.

“We definitely would like a speaker, preferably from the FDA for the interest group at Annual,” Ginsbury said. “And we have asked our participants if any of them would like to address the group. We have asked participants to prioritize issues and will select one or two for drill down at Annual.”

Continued at bottom of page 46

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North America

U.S. FDA Issues Draft GDUFA Guidance

The U.S. FDA announced availability of a draft guidance, titled “Initial Completeness Assessments for Type II API DMFs Under GDUFA.” This guidance is intended to clarify criteria the Agency will use in the initial completeness assessment required for holders of certain drug master files that are referenced in generic drug applications or in amendments or prior approval supplements to these applications, under GDUFA. Comment are due by December 31.

U.S. FDA Announces Notification Requirement for Generic Facilities

For fiscal year 2013, the U.S. FDA now requires generic drug facilities, and other sites and organizations identified in generic drug submissions, to provide identification information to the Agency.

The Agency has published a notice outlining the types of facilities required to self-identify. These include component manufacturers, packaging facilities and testing labs.

The information that should be included is identified in the GDUFA SPL Industry Technical Specification Information document, and includes the name and contact information for both the registrant owner and the facility if they are two different entities. The Agency also

requires information about the type of business operations, and if necessary, the DUNS number and FEI number.

The information can be submitted electronically through the following tools: eSubmitter, Xforms, internally designed software that uses SPL technical specifications, and other commercially available applications.

Europe

EMA Begins Infringement Procedure to Investigate Roche Non-Compliance

EMA has begun an infringement procedure against Roche Registration Ltd to investigate allegations the company did not comply with pharmacovigilance obligations pertaining to 19 medicines. The Agency will investigate the allegations under Regulation (EC) No 658/2007 and will report the outcome of the investigation to the European Commission, which has the authority to impose fines or periodic penalty payments if it finds that Roche has committed infringement against the pharmacovigilance obligations.

Roche and the Commission have been informed that EMA has started infringement proceedings.

Amendments Impacting Centrally Authorized Medicines Now in Effect

As of, November 2, amendments to Eu-

Key Regulatory Dates
Comments Due
December 31 — U.S. FDA Draft Guidance on Initial Completeness Assessments Under GDUFA Available

ropean Variations Regulation concerning centrally authorized medicines are now in effect, per Commission Regulation (EU) No 712/2012. Changes effecting authorized medicines include: decision-making process changes that allow for changes important for public health are mirrored in marketing authorizations within two months (other changes can be reflected in regular updates provided within one year), and inclusion of compliance statements that mention the agreed-upon and completed pediatric investigation plan within the marketing authorization.

EMA will be providing an updated post-authorization procedural advice containing the Variations Regulation changes within the next few weeks.

Since Jan. 1, 2010, Variations Regulation provides instructions for handling applications from marketing-authorization holders with changes to existing marketing authorizations. ☞

Voices of the Board continued from page 52

driven activities? A good way of doing this is to speak “in a language” that works well for the audience and the company. Link the quality messages to safety, efficiency and money. Speak about financial benefits and use the term Operational Excellence (or whichever words translate into driving continual improvement and prevention of issues at your organization).

The *PDA Cost of Poor Quality* survey was mentioned as a first step to create a model for explaining the benefits of systematically assuring consistent quality on a daily basis in accord with the process validation and ICH Q10 lifecycle concepts.

Moving Forward

The dialog at the breakout sessions could

have gone on much longer, and we believe it is important that we continue these discussions to take up the challenge **Janet Woodcock** and FDA have given the industry to improve compliance and for us to improve our business.

PDA will continue to actively lead and facilitate this discussion connecting people, science and regulation. ☞

Explore Manufacturing Trends at the 2013 Annual Meeting

2013 Annual PDA Meeting • Orlando, Fla. • April 15-17 • www.pda.org/annual2013

Miguel Montalvo, Expert Validation Consulting, Inc.

As we get closer to the end of 2012, it is my pleasure to invite you to attend our next Annual Meeting. Our theme for next year is *Modern Sterile Product Manufacturing – Exploring Best Practices and Seeking New Approaches*.

We are always looking for the best practices in everything that we do within our industry, especially if that practice involves a new or modified approach to our current processes. The most effective way of learning about these best practices and new approaches is by attending industry-focused meetings where these are presented and provide opportunities for expert speakers to address any questions or concerns you may have. The PDA Annual Meeting provides this type of

opportunity in addition to offering networking events, among other benefits.

Learn to Adapt to the Global Regulatory Environment

Learning about best practices and new approaches is not just important from the standpoint of desirable outcomes but it's also a necessity in the current competitive and globalized environment. For us to remain competitive, we need to become more efficient and effective; applying best practices and approaches is definitely one path to accomplish that goal. The meet-

- **Track 1:** “Biological Sciences”
- **Track 2:** “Sterile Product Manufacturing”
- **Track 3:** “Quality Systems”

Within the track format, individual sessions will address specific topics including:

- Current Trends in Process Validation
- Innovative Approaches to Sterile Product Packaging
- Biosimilars
- Contemporary Practice in the Manufacture of Sterile Products

Come network with old friends and meet new ones



Don't miss out on the fun! A performer from PDA's last Annual Meeting in Orlando, FL from 2010.

ing will provide presentations by industry leaders on these methods and the opportunity to share opinions and concerns about the topics being presented.

You will not want to miss this opportunity to discuss these critical topics to our industry and to share your experiences and concerns with top industry personnel and scientists in order to shape the future of our business. In addition, the meeting will provide an extremely valuable networking opportunity for experienced management personnel as well as novices to our operations and scientific functions. This is the most important PDA event throughout the year and we expect a large portion of our globalized membership to be present. Come network with old friends and meet new ones.

Follow the Topics That Interest You

The meeting will be conducted in our traditional format with three parallel concurrent sessions as follows:

- Outsourcing Management
- Advances in Single-use Technology Applications
- Viral Safety Strategies

As at every Annual Meeting, our interest groups will also conduct their independent sessions to discuss the latest advances and news on each particular area with participation from industry experts in their field.

In addition to the formal conference proceedings we have put together an impressive choice of optional and fun events beginning with the 7th Annual PDA Golf Tournament and the 7th Annual Fun Walk/Run on Sunday, April 14. Make your conference experience a well-rounded one by taking part in these networking activities.

We all look forward to seeing you in my home town of Orlando, Fla. where everything is certainly “Magical”. 🌴

Make a Lasting Impression During Preapproval Inspection continued from page 33



validated autoclave loads, issues with cleaning validation, and ignored building alarms.

Of the latter, she said, “please don’t tell the FDA inspectors those tens of thousands of alarms are nuisance alarms,” citing events that her teams have encountered.

With regard to in-vitro diagnostic test kits, her teams have encountered lack of design controls, incomplete equipment qualifications, lack of in-process controls, undefined management responsibilities, missing quality oversight, no control over critical suppliers, little to no training, inadequate document control, poor CAPA execution, inadequate bioburden monitoring, and insufficient preventive maintenance. Teams inspecting veterinary medicines facilities have come across systemic mold, biofilms, inadequate cleaning validation, poor equipment maintenance, poor equipment maintenance, co-eluting impurity peaks (HPLC) in analytical method validation, reference standards improperly stored/labeled, and not filing three-day field alerts for OOS.

In the end, both Trudel and Severy concurred on the importance of adequate preparation and communication, both prior, during, and following preapproval inspection. FDASIA expands regulatory requirements for inspections, particularly of foreign facilities, so it makes sense for regulators and industry to work together to make the inspection process smoother for both parties.

About the Experts

Lisa Severy, Senior Quality Regulatory Manager has worked for Baxter for more than 30 years in various roles within the Quality organization, including QC Laboratory, Quality Assurance Management and Quality/Regulatory Compliance. Since 1994, Lisa has led inspection preparation and management of the inspection process for several pre-approval inspections, in addition to many routine, GMP inspections at two major biological manufacturing sites. Currently, she works at Baxter’s BioScience division headquarters, continuing to provide global support for inspection preparedness and guidance to the manufacturing sites regarding quality/regulatory compliance.



Nicole Trudel has eight years of experience at CBER’s Division of Manufacturing and Product Quality in the Office of Compliance and Biologics Quality. Her experience includes a wide range of CMC and facility reviews and inspections for biologics license applications and supplements relative to bacterial and viral vaccines, recombinant products, in vitro diagnostic test kits, plasma fractionated products, allergenic extracts, and cord blood. She also has experience in the review and inspection of BLA and Premarket Applications for IVD test kits. Nicole also supports internal and external training in her various areas of technical expertise and has participated in numerous policy groups addressing CGMP, harmonization and inspection related issues. She holds a B.S. degree in Mechanical Engineering. 🇺🇸



The Parenteral Drug Association presents...

2013 PDA Europe Workshop on Single Use Systems for Pharmaceutical Applications

The workshop addresses the importance of Single Use Systems (SUS) in pharmaceutical development and manufacturing.

Based on the Technical Report, you will hear about advantages, disadvantages and how you can make best use of SUS.

Benefit from case studies, discussions with regulators and industry experts. Get in direct contact with the different suppliers of SUS technology.



15-16 January
Milano | Italy

15-16 JANUARY | WORKSHOP | EXHIBITION

<https://europe.pda.org/SingleUse2013>

Experts Offer Guidance on Delivering Vaccines Worldwide

PDA/FDA Vaccines Conference • Bethesda, Md. • Dec. 3-4 • www.pda.org/vaccines

While advances in science and technology are leading to the development of a wide array of new vaccines and novel manufacturing approaches, the vaccine industry continues to face technical, logistical and regulatory challenges. This is especially true for vaccines needed in developing countries and other international markets. We invite you to come to the *PDA/FDA Vaccines Conference* to hear about novel industry approaches for supplying vaccines along to domestic and international markets. Industry and regulatory experts will also discuss various approaches to manufacturing and distribution issues.

This two day event includes many information-packed sessions, vital for today's vaccine professional. Here are just some of the sessions that will be of high interest:

- Learn how to navigate the multiple regulatory requirements and guidances for adventitious agent testing and cell

substrate characterization with **Arifa Khan**, PhD, Supervisory Microbiologist, from CBER, U.S. FDA and **Laurient Mallet**, PhD, Head of Analytical Research and Development, North America, of Sanofi Pasteur, Ltd.,

- Hear "Regulatory Perspectives on QbD during Vaccine Development" from **Philip Krause**, MD, Deputy Director, Office of Vaccines Research and Review, CBER, FDA,
- Participate in a session on hot topics in regulation, featuring presentations on "Rapid Mycoplasma Detection Methods" from **Vladimir Chizhikov**, PhD, Chemist, CBER, FDA, and "Direct Recall Classification" from FDA speakers,
- View a presentation from **Michael B. Havert**, PhD, Biologist, Office of Cell, Tissue and Gene Therapies, CBER,

FDA on the "Evolution of Regulatory Framework," and

- Review global regulatory challenges with **Marion Gruber**, PhD, Director, OVR, CBER, FDA by understanding the regulatory environments around the globe including licensing requirements, immunizations schedules, lot release, and pharmacopeial specifications.

Please join us for these topics and more! This is a must-attend event for all involved in the manufacturing and testing of vaccines for preventive and therapeutic purposes. We encourage pharmaceutical and biopharmaceutical professionals with responsibilities in development, manufacturing, preclinical, quality assurance, quality control and regulatory affairs to participate.

Following the conference, PDA's Training and Research Institute will also hold two one-day courses on Dec. 5-6. 🌐

Interest Group Corner continued from page 40

"We had a number of issues that came up during our talk and I think they have a number of topics they want to address," Schniepp said. "It will be exciting to see where we can take this group. There are a lot of issues facing us... I'm really excited that PDA has decided that it's a worthwhile subject to be starting to address."

Both she and Ginsbury agree that the interest group is focusing on a growing area of the industry.

"I do think that contract manufacturing is going to continue to grow in the industry," said Schniepp. "I think it services not only the Big Pharma but there's an emerging pharma where there are just virtual companies out there working on one molecule. And those companies are going to take advantage of the entire con-

tract supply chain from their clinical trials to the commercialization of the product."

About the Experts

Karen Ginsbury is a London trained pharmacist, with a master's degree in microbiology. Expert in all aspects of cleanrooms and microbiology, she has a second area of expertise in the GMP



manufacture of investigational drugs and is currently co-editing a PDA Technical Report on the topic. With over 20 years of experience in the industry, Karen has hands-on experience of quality assurance and setting up GMP compliant quality systems. She regularly lectures around the world on related topics.

Karen is an active PDA volunteer, serving on the *PDA Letter* Editorial Committee and the

Regulatory Affairs and Quality Advisory Board.

Sue Schniepp has over 24 years of experience in quality assurance, for both the food and pharmaceutical industries, and is currently Vice President, Quality and Regulatory Affairs for Allergy Laboratories.



She has a degree in microbiology from Northern Illinois University and began her career in 1980 as a microbiologist in the food industry where she first used the U.S. Pharmacopeia. In 1984, she transitioned to the pharmaceutical industry as an R&D Microbiologist.

Sue is an active PDA volunteer, serving on the *PDA Letter* Editorial Committee and the Regulatory Affairs and Quality Advisory Board. She also serves on the PDA/FDA Joint Regulatory Conference Program Planning Committee, which she has chaired. 🌐

2013 PDA ANNUAL MEETING

Modern Sterile Product
Manufacturing –
Exploring Best Practices
and Seeking New Approaches



April 15-17, 2013 | The Peabody Orlando | Orlando, Florida

CALL FOR POSTERS

The 2013 PDA Annual Meeting Program Planning Committee encourages you to submit an abstract for a one-day poster presentation at the 2013 PDA Annual Meeting, which will be held on April 15-17, 2013 in Orlando. Abstracts must be noncommercial, describe developments, strategies or work and significantly contribute to the body of knowledge relating to biopharmaceutical manufacturing, process knowledge, quality management and technology. Abstracts related to sterile or related product manufacture are preferable, but those addressing other technologies are welcome. All abstracts will be reviewed by the Program Planning Committee for consideration.

Suggested topics include, but are not limited to:

BIOLOGICAL SCIENCES

- Microbial Control in the Manufacturing Environment
- Bio-film
- Combination Products
- Container Closure Integrity
- Green/Sustainable Manufacturing
- PAT
- Cell Culture Processes
- Viral Clearance
- Purification Process

STERILE PRODUCT MANUFACTURING

- Diagnostics
- Challenges in Quality for ACIs
- Challenges in Manufacturing
- Expiration of Products, Logistics and Shipping
- Stem Cells
- Single-use Technology

QUALITY SYSTEMS

- Testing Characterization, Stability
- Room Decontamination and H2O2
- Upstream/Downstream: Chromatography
- Cold Chain
- Sterilization
- Bio-burden/Bio-film
- Mycoplasma/Virus
- Process Validation
- Cleaning Methods and Validation

Abstracts must be received by January 14, 2013 for consideration.

You will be advised in writing of the status of your abstract by **February 8, 2013**. Poster presenters are required to register as a *full conference* attendee at the rate of \$1795 member/\$2044 nonmember. *Exhibit only* registrants are eligible to present a poster by registering as a full conference participant. In order to be listed in the final program, your full conference registration must be received no later than **March 1, 2013**. After March 1, the prevailing registration fees and policies apply.

Visit www.pdaannualmeeting.org/2013CFP to submit an abstract.

Please include the following information with each abstract:

- Presenter's name
- Presenter's professional title
- Presenter's full mailing address
- Presenter's e-mail address
- Presenter's phone number
- 2-3 paragraph abstract, summarizing your topic and the appropriate forum (case study, discussion, traditional, panel, etc.)
- Take-home benefits
- Presentation objectives

For more information, please contact Melissa Pazornik, Coordinator, Speaker & Logistics Assistant via e-mail at Pazornik@pda.org or phone at (301) 656-5900 ext. 221.

2012 Closes With a Successful Year for TRI

Bob Dana, PDA

It's a beautiful October afternoon in upstate New York – bright blue skies, warm sun but enough of a chill in the air to remind me that another year is coming to close. Recognizing that, it's time for me to reflect on 2012 and look back at what it meant for PDA's Training and Research Institute (TRI).

By any measure, 2012 was a very busy and successful year for TRI. We had unprecedented attendance at training courses, led by our flagship "Aseptic Processing Training Program." Our in-house training programs continued to grow, including a multi-session course, "Practical Aspects of Aseptic Processing," which was delivered to one company. We also enjoyed very strong attendance at our lecture course series, hosted in conjunction with PDA conferences. To better serve our students and members, we added new staff to our team. These accomplishments and additions allowed us to contribute to the successes PDA enjoyed in 2012.

We got the year started quickly with the first week of Session 1 of our "Aseptic Processing Training Program" starting Jan. 9. This was the first of five sessions in 2012, all of which sold out. In fact, every session for the year was sold out by March—a new record. This course justifiably remains incredibly popular and provides a unique opportunity for the participants to gain insights and hands-on experience with the complexities associated with aseptic processing.

Based on the success of hosting several themed weeks last year at our training facility, we continued providing topic-focused, week-long training opportunities this year. In March, we hosted Lyophilization Week with two popular courses: "Fundamentals of Lyophilization" taught by **Ed Trappler**, and "Validation of Lyophilization" taught by **Karen Bossert** and **Barbara Berglund**. Students could register for one course or both; many took advantage of the op-

portunity to have intensive training on one topic by staying the week and taking both courses. Altogether, Lyophilization Week proved successful once again with almost 50 registrations.

In Phoenix, Arizona at the 2013 *PDA Annual Meeting*, faculty member Ed Trappler was awarded the James P. Agaloco Award. This award is presented annually to the PDA TRI faculty member who exemplifies outstanding performance in education. Congratulations, Ed, and thank you for all you do for TRI and our students. Several of our Annual Meeting courses exceeded our expectations, including "Manual Aseptic Processing," taught by **Carol Lampe**; "Quality Risk Management" taught by **Jeff Hartman** and **Emma Ramnarine**; and "Process Validation and Verification" with faculty members **Scott Bozzone**, and **Wendy Lambert** providing the instruction. This marked the first time Jeff, Emma and Wendy had taught courses for PDA and we are looking forward to their future participation in these and other courses.

This summer, we had the opportunity to present courses at PDA's *Virus and TSE Safety Conference*; both "Viral Contamination and Remediation" and "Basic Virology" drew good enrollments. We also presented courses at the *PDA/FDA Conference on Glass Quality* and, once again, "Identification and Classification of Nonconformities in Molded and Tubular Glass Containers" was a sellout.

We closed out our summer "on-the-road" events with three courses at PDA's *Conference on Sterile Technology* in Chicago. Both our courses on "Moist Heat Sterilization" and "Dry Heat Validation" exceeded our expectations, and our "Parametric Release" course also had over ten students hear instructor **Mike Sadowski** discuss the critical elements associated with this technology.

In September, we traveled up Interstate 95 to Baltimore where we presented six

courses at the *PDA/FDA Joint Regulatory Conference*, including the new courses: "Good Distribution Practices for the Pharmaceutical Supply Chain" and "Application of Phase-Appropriate GMP to the Development of Protein Bulk Drug Substances." Both "Application of a Quality Systems Approach to Pharmaceutical GMPs," taught by **Miguel Montalvo**, and "Development of Qualification and Validation Protocols - A Risk Management Approach" with **Hal Baseman**, were particularly well-received.

In October, PDA once again offered three conferences, starting with the *Biennial Training Conference*. This conference provides a forum for professionals who develop and present training programs for our industry. All three courses at this conference; "Qualifying Your Subject Matter Experts as Trainers" (**Vivian Bringslimark**), "FDA Inspection Readiness for a Training Systems Audit" (**Barbara Van der Schalie**) and "Learning, Knowledge Management and Impact – Moving from Theory to Practice" (**Jim Vesper**); met or exceeded our expectations. It seems clear that trainers realize the value of being trained!

We closed out our lecture courses for 2012 with offerings at the *Pre-filled Syringes and Injection Devices Conference*, the *7th Annual Global Conference on Pharmaceutical Microbiology*, the *PDA/FDA Supply Chain Conference*, and the *PDA/FDA Vaccines Conference*. All in all, it was a very successful year for our lecture courses with the details being capably managed by **Stephanie Ko**.

While all this was going on with our lecture courses, we were also busy at the TRI facility in Bethesda with our laboratory courses. In addition to our flagship "Aseptic Processing Training Program," TRI delivered a number of hands-on lab courses. These courses, combined with a lecture component, provide plenty of opportunity for the students to put into

practice in the lab what they learn in the classroom.

Responding to past student feedback, we presented our “An Introduction to Visual Inspection” class twice. The combined enrollment for the two sessions showed that there is still plenty of interest in this topic in our industry. If you are involved in this technology, I urge you to consider enrolling in one of the two sessions we’ll be offering in 2013.

We offered two new courses on virus-related technologies, and were excited that FDA scientists **Kurt Brorson** and **Scott Lute** served as the teachers. Based on this year’s experiences, we will roll “Preparation of Virus Spikes Used for Viral Clearance Studies” and “Virus Filtration” into a comprehensive three-day course in 2013.

Longtime PDA instructors **Maik Jornitz** and **Wayne Garafola** delivered two courses on filtration technologies during our 2012 Filtration Week in August. “Filters and Filtration in the Biopharmaceutical Industry – Basics Course” provided students the fundamentals of filtration theory and design, and “Filters and Filtration in the Biopharmaceutical Industry – Advanced Course” provided plenty of hands-on experiences for the students as they got experience in what happens when, as Jornitz likes to say, “We put some sand in the gear box.” Almost 30 students participated and benefited from the knowledge of these two instructors.

Building on the successes of our “Aseptic Processing Training Program,” as well as the lessons we learned last year from the initial offering, we again presented “Quality Systems for Aseptic Processing.” This course, taught by co-lead instructors **Dave Matsuhiro** and Hal Baseman, as well as other faculty, takes the students a step beyond the concepts presented in the two-week aseptic training program, and provides students the tools to answer the question, “What do I do when things go wrong?” This year, a capacity group of 17 students participated.

Also, we offered “Validation of Biotechnology-related Cleaning Processes” along with what I believe will be a really unique course titled “Risk-based Qualification of Sterile Drug Product Manufacturing Systems.” This course, developed and presented by **Phil DeSantis** and **Walter Henkels**, takes the students through the design and execution of qualification and validation protocols using the equipment and utilities in TRI’s clean room, providing an invaluable experience for individuals involved in these activities in their own daily jobs.

In September, we were really excited to offer hands-on training to FDA staff when 15 members of CDER exclusively participated in “Practical Aspects of Aseptic Processing.”

In addition to our entire faculty, Lab Manager **James Wamsley** received help and support from laboratory technician **Gerard Cornejo** and our newly hired Coordinator of Laboratory Education **Jake Wolpe**. Gerard spent just over six months with us before leaving in mid-October to return to school and Jake, newly graduated from James Madison University, joined us in late September. We benefited from the hard work of our ►



PDA Conference Recordings – Interactive Online Learning

PDA’s Conference Recordings allow you to affordably hear from today’s top presenters in the bio/pharmaceutical industry with no traveling!

Recordings from PDA’s events through September 2012 are now available for purchase. The events include:

PDA/FDA Joint Regulatory Conference and Responsibilities of Executive Management ICHQ10 Workshop Session Recordings

Recordings from the entire conference and workshop are available for purchase for **\$340 Member/\$380 Nonmember**. Price of recordings includes:

- Fourteen (14) recorded sessions from the 2012 PDA/FDA JRC and six (6) sessions from the ICHQ10 Workshop
- Access to 58 downloadable presentation handouts
- Unlimited playback of the recordings for **90 days from receipt of login information**.

PDA/FDA Glass Quality Conference

Recordings from the entire conference are available for purchase for **\$255 for members and \$295 for nonmembers**. Price of recordings includes:

- All nine (9) sessions from the 2012 Conference
- Access to 24 downloadable presentation handouts
- Unlimited access to all session recordings for **60 days from receipt of login information**.

Innovation & Best Practices on Sterile Technology Conference

Recordings from the entire conference are available for purchase for **\$215 Member/\$255 Nonmember**. Price of recordings includes:

- All eight (8) recorded sessions from the 2012 Conference
- Access to 19 downloadable presentation handouts and the A-VAX Case Study
- Unlimited access to all session recordings for **60 days from receipt of login information**.

Members Save More: Receive 30% off the member price of a single event recording or session recordings bundle when you purchase or renew your PDA Membership!

**For more information on all PDA conference recordings please visit:
www.pda.org/webseminars**



Parenteral Drug Association Training and Research Institute (PDA TRI)

Customized Training at Your Facility or Ours



PDA TRI can work with you to bring custom “in-house” training solutions and expert instructors right to your doorstep. Get training solutions that meet your specific needs while saving time and money on travel. If your offices are not conducive to training, PDA TRI can host your programs in our facility located in Bethesda, MD. Our state-of-the-art facility includes an aseptic processing suite with a filling room, component prep lab and gowning/degowning areas, clean-in-place lab, microbiology lab, biotechnology lab, classrooms and student break areas.

We can deliver one of our existing training courses to your organization or we can work with you to develop the custom training you need. Below find a list of available subject areas covered by TRI training.



Aseptic

Quality and Regulatory Affairs

Biotech

Specialized

Environmental Monitoring

Training

Filtration

Validation

Microbiology



We look forward to bringing our expert-led pharmaceutical and biopharmaceutical training to you.

Contact us to discuss your specific needs:

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Senior Vice President Quality and Regulatory Affairs
and PDA Training and Research Institute

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dana@pda.org

For more information please visit www.pda.org/courses

*In fact, every session for the year was sold out by
March — a new record*

first summer intern, **Kyle Nakashima**, who spent six weeks working in the labs with James and Dave Matsuhira before returning to school in September. The experience provided Kyle the opportunity to learn something about the pharmaceutical industry and also provided PDA with some additional lab support for our aseptic processing training.

The year just ending marked the beginning of a new strategy for TRI's education programs. In 2012, we presented over 20 courses based on PDA-owned material. By strengthening the partnership between TRI and PDA's Scientific and Regulatory Affairs department, led by **Rich Levy**, we were able to leverage the material owned by PDA and build it into education courses only available from TRI. The course content was created based on the content of the Technical Reports by Rich, his staff and the teams that developed the Technical Reports. TRI staff, working with consultant **Bethanne Bond** and the faculty, who was drawn from the teams that developed the Technical Reports, then developed the actual course materials. This approach resulted in a series of high-quality courses, developed and presented by the experts who put the Technical Reports together, and presented in a brand-identity format which tied them all together. We owe a big thank you to Rich and his staff: **Vince Anicetti**, **Josh Eaton**, **Jim Lyda** and **Janie Miller**, as well as the instructors and Technical Report task forces in making this strategy a reality.

Our in-house training programs continued to flourish in 2012, demonstrating the value of being able to bring customized educational content right to the companies that need the training. Of particular note this year was a request to provide multiple sessions of the training course, "Practical Aspects of Aseptic Processing," to a single company. Fulfill-

ing this request, in addition to all the other activities we had already scheduled for 2012, was a daunting task. Thanks to a lot of hard work and dedication by the TRI staff, most notably James, as well as TRI instructors Hal Baseman, **Cheryl Custard**, Carol Lampe, **Joe Lasich**, Jim Lyda and **Rainer Newman**, we delivered a series of one-week sessions which, by all reports, were very well received and beneficial to the company. And this was but one of several in-house programs we delivered in 2012.

So that about brings down the curtain on the year. By any measure, it was a very successful one. None of this could have been accomplished without the hard work of a lot of people. I have tried to recognize and acknowledge them in this article. However, there is another group of people without whom we could not have had the success we had: and that is our students. There were almost 1,400 of you this year, and all I can say is thank you for your support of our educational efforts. We present our courses to help you and it's extremely gratifying to see that you appreciate our efforts.

I'd like to close by wishing each of you, the readers, a safe, happy, healthy and prosperous 2013. I hope to see many of you at one of our TRI courses next year.

PDA's Who's Who

Vince Anicetti, PDA Fellow

Hal Baseman, COO, Valsource

Barbara Berglund, Manager, QA, Boehringer Ingelheim

Bethanne Bond, Consultant

Karen Bossert, PhD, Vice President, Lyophilization Technology

Scott Bozzone, PhD, Sr. Manager, Quality Systems and Technical Services-Validation, Pfizer

Vivian Bringslimark, President, HPIS Consulting

Kurt Brorson, PhD, Staff Scientist, FDA

Gerard Cornejo, Laboratory Technician, TRI, PDA

Cheryl Custard

Phil DeSantis, Principal Consultant, DeSantis Consulting Associates

Josh Eaton, Sr. Project Manager, Scientific & Regulatory Affairs, PDA

Wayne Garafola, Application Specialist, Sartorius

Jeff Hartman, Director, Validation Quality Assurance, Merck

Walter Henkels, ConcordiaValSource

Maik Jornitz, Vice President, G-Con Manuf

Stephanie Ko, Sr. Manager, Lecture Education, TRI, PDA

Joe Lasich, Consultant

Wendy Lambert, Director, Quality and Regulatory, Abbott Labs

Carol Lampe, Sr. Consultant, J.M. Hansen & Associates

Rich Levy, PhD, Senior Vice President, Scientific and Regulatory Affairs, PDA

Scott Lute, Biologist, CDER, FDA

Jim Lyda, Senior Science & Reg. Affairs Advisor, PDA

Dave Matsuhira, President, Cleanroom Compliance

Janie Miller, Sr. Project Manager, Scientific and Regulatory Affairs, PDA

Miguel Montalvo, President, Expert Validation Consulting Inc.

Kyle Nakashima, Intern, TRI, PDA

Rainer Newman, Consultant

Emma Ramnarine, Sr. Manager, Genentech

Mike Sadowski, Director, Sterile Manufacturing Support, Baxter SA

Ed Trappler, President, Lyophilization Technology

Barbara Van der Schalie, Clinical Training Manager, SAIC-Frederick

Jim Vesper, President, LearningPlus

James Wamsley, Senior Manager, Laboratory Education, TRI, PDA

Jake Wolpe, Coordinator, Laboratory Education, TRI, PDA 



PDA Chair Anders Vinther, PhD

Top Industry Leaders Talk Best Practices for Pharmaceutical Quality Systems

At the 2012 PDA/FDA workshop, *Responsibilities of Executive Management – Implementing the Principles of ICH Q10*, 150 industry and health authority senior leaders and experts shared best practices on the pharmaceutical quality system (PQS). **Steven Lynn**, Director, U.S. FDA, **Rick Friedman**, Associate Director, FDA, **Jennifer Magnani**, Associate Director of Quality, Genentech and **Anders Vinther**, PhD, Vice President Quality Biologics, Genentech, and PDA Chair, co-chaired the event.

At the workshop, four highly engaging break-out sessions covered the topics of what works and what doesn't in creating a PQS, which metrics are useful and what types of governance models are effective. An industry and a FDA representative facilitated each session. The dialog was very rich, with many great ideas and experiences shared.

Proactive Metrics

One of the most insightful conclusions reached during the sessions involved moving away from reactive metrics to proactive metrics. It is important for companies to engage in dialogue regarding the “why” behind red (stop, risk) and yellow (caution)

metrics. If the company culture is that of ‘must have greens,’ the company greatly reduces the dialog that can improve the business on a continual basis.

The metrics should truly reflect the state of control, provide relevant feedback loops, periodically be reviewed for appropriateness and suitability and communicated broadly, e.g., on visual performance boards, etc.

The attendees spent some time talking about metrics that show whether or not the company has ‘the right’ quality culture.

It was also acknowledged that the potential to drive improvements by having a solid cost-of-poor-quality model in place with a robust feedback loop was not fully understood by company senior leaders.

Some specific metrics discussed were:

- Investigations: time to initiate, lack of recurrence, adherence to closure time, percentage of root cause found
- CAPA: lack of recurrence, number of time line extensions, adherence to closure time
- Product disposition cycle time
- Risk management: change in risk profile, effectiveness, number of self-identified risks (speak-up culture), comparative metrics site-to-site
- Right First Time: avoid linking to performance incentives if this drives the wrong behavior
- Process capabilities: variability like CpK and other variability metrics
- Cost of Quality: leading versus lagging indicators – use simple models
- Organizational health metrics as a measure of quality culture: safety metrics, employee satisfaction and engagement, talent retention, adherence to training plans, number of employee suggestions and how many implemented
- Governance: no ‘surprises’ coming out of audit and inspectional findings – i.e., issues should already have been identified and included in improvement plans

The common theme for governance and organizational structure was that of integrating the business teams more (quality, operations, etc), co-locate them and share common goals and objectives. This eliminates silos and improves product quality and compliance when done the right way.

It is also important for the company to dedicate time and resources to process improvements and preventive actions rather than focusing on the corrective part of the CAPA system only.

Where many companies are still struggling is the transition or migration into a culture of “quality owned by all.” Attendees discussed whether the quality organization most often leads investigations into quality issues that originates from manufacturing processes (and therefore probably should be called manufacturing issues rather than quality issues) or have operation taken more ownership? Several attendees said the shift needs to be a deliberate change that starts at the top in the organization. The shift in culture should also be encouraged and stimulated by linking the right quality mindset and actions to the company rewards and recognition system.

Speaking the language

How do you “sell the message of quality?” Or in other words, how does the rest of the organization better appreciate and support quality

Continued at bottom of page 43



Calling All Active PDA Members Vote Now!

Online Voting Opens September 10th for the 2013 PDA Board of Directors Election

PDA members, online voting will open on September 10th for the 2013 **PDA Board of Directors Election**, we encourage you to take a moment and vote for your candidates of choice.

To vote is easy, just follow the instructions below. You will need your PDA Member ID and last name to log in.

All PDA members in good standing as of **midnight on August 31, 2012 are eligible to vote**. Voting for this election will close at **11:59 p.m. EST on November 11, 2012**. All votes cast after this date and time will not be accepted.

If you need assistance please contact the PDA Membership Service Department at +1 (301) 656-5900 ext. 119 or howe@pda.org.

Thank you for being a valued PDA member and voting!



Instructions for Voting:

- Go to www.pda.org/vote
- Log into the system using your PDA Member ID and last name
- Please read the instructions for each question carefully
- Review the choices for each position then select a candidate for that position
- When you are done voting, review your selection and then check the participant consent box and click on the "SUBMIT" button
- You have now completed the voting process
- You can view and print your receipt or exit the PDA eBallot System

Thank you for your participation in this important election process.

Another Volume Year in the Books

What a year for the *PDA Letter*. We started off covering human factors testing in the January issue and are ending it with articles on Quality by Design and Quality Systems. In between, we published feature articles on job aids, rapid microbial methods, prescription distribution licenses, biofilms, biosimilars regulations, and more. We thank the many authors who graced our pages with their work, and we are ever grateful for the hard work of the *PDA Letter* Editorial Committee for suggesting topics, authoring articles, reviewing articles and finding authors. It is that time of the year to say goodbye to a number of PLEC members who have served their two-year terms. Departing at the end of the year are: **Sue Schneipp, Sandra Zoghbi-Gay, Winston Brown, Jose Caraballo, Robert Darius, Martha Folmsbee, Janeen Skutnik-Wilkinson** and **Anastasia Lolos**. I thank all of these fellow committee members for their dedication to PDA and the Letter, in particular. Many of these volunteers are also involved in other PDA activities, and they all are eligible to serve on PLEC again in the future.

We are currently looking for dedicated volunteers to serve a two-year term on PLEC. If you are interested, please email me or **Rebecca Stauffer**. Tell us why you want to serve on PLEC, and we will get back to you by the end of the year.

We are always looking for authors, and our editorial calendar for 2013 has a lot of hot topics. We are accepting 1500-2000 word articles on drug shortages, process validation, career advancement, sterile processing (any aspect), consent decrees, disposable systems, and filtration validation. If you would like to author an article on any of these topics, contact me with your proposal. The PLEC reviews proposals for articles and provides outstanding feedback.

Speaking of change, it was with great sadness that I said goodbye to **Emily Hough**, my assistant in putting together the *PDA Letter* since 2007. Emily was a great contributor to the *PDA Letter*, authoring and editing many articles and managing the PLEC. She is still at PDA plying her trade for the Marketing Department, so I continue to enjoy seeing her and hearing all about her nephews!

Rebecca Stauffer has done a great job since joining the Letter staff in September. This issue alone contains a number of articles by Rebecca. She has attended the *2012 PDA/FDA Joint Regulatory Conference* and the *7th Annual Pharmaceutical Microbiology Conference*, and will be at several more before year's end. I look forward to even more contribution from Rebecca in 2013.

Well, as we close out 2012, I can't say how much I look forward to 2013, which will be my tenth year at the helm of the *PDA Letter*. It is a pleasure working with the various members and PDA staff who make the Letter possible. Please, never hesitate to send us an email if you have problems, see errors, want to contribute, or just want to tell us what you like and don't like about the Letter.

See you all in 2013! 🍷

PDA Letter

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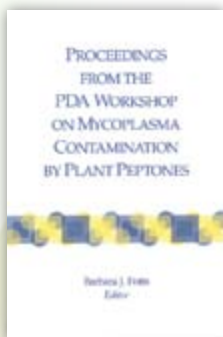
Correction: The Honor Awards Recipients listing in the September and October issues should have indicated that they were 2011 award winners recognized at the *2012 PDA Annual Meeting*.

PDA Bookstore 2012 Clearance Sale



The PDA Bookstore 2012 clearance sale is going on now! **Save 50% now through November 30, 2012.** Enter Coupon Code **2012clearance** during checkout to activate your savings.

Check out a sample of some publications now on sale below!

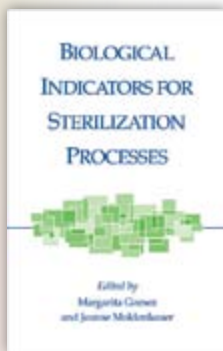


Proceedings from the PDA Workshop on Mycoplasma Contamination by Plant Peptones

The proceedings contain important presentations which will provide readers with recent information offered by subject matter experts who presented at the 2005 PDA Workshop on the contamination of plant peptones. 2007, 257 pages.

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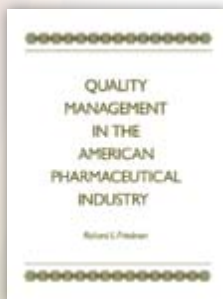
Biological Indicators for Sterilization Processes

Editors: Margarita Gomez and Jeanne Moldenhauer

This book will be of great interest to laboratory supervisors, regulatory and compliance personnel, validation specialists and professionals engaged in other aspects of pharmaceutical and biopharmaceutical manufacturing. 2008, 536 pages.

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Quality Management in the American Pharmaceutical Industry (print version)

Author: Richard Friedman

Chapter excerpted from the book Pharmaceutical Quality. 2006, Softcover, 40 pages.

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