People • Science • Regulation

PDA Letter

Volume XLIX • Issue 1 www.pda.org/pdaletter January 2013

Proposed CDER Office Seeks to Change Quality Paradigm in Industry

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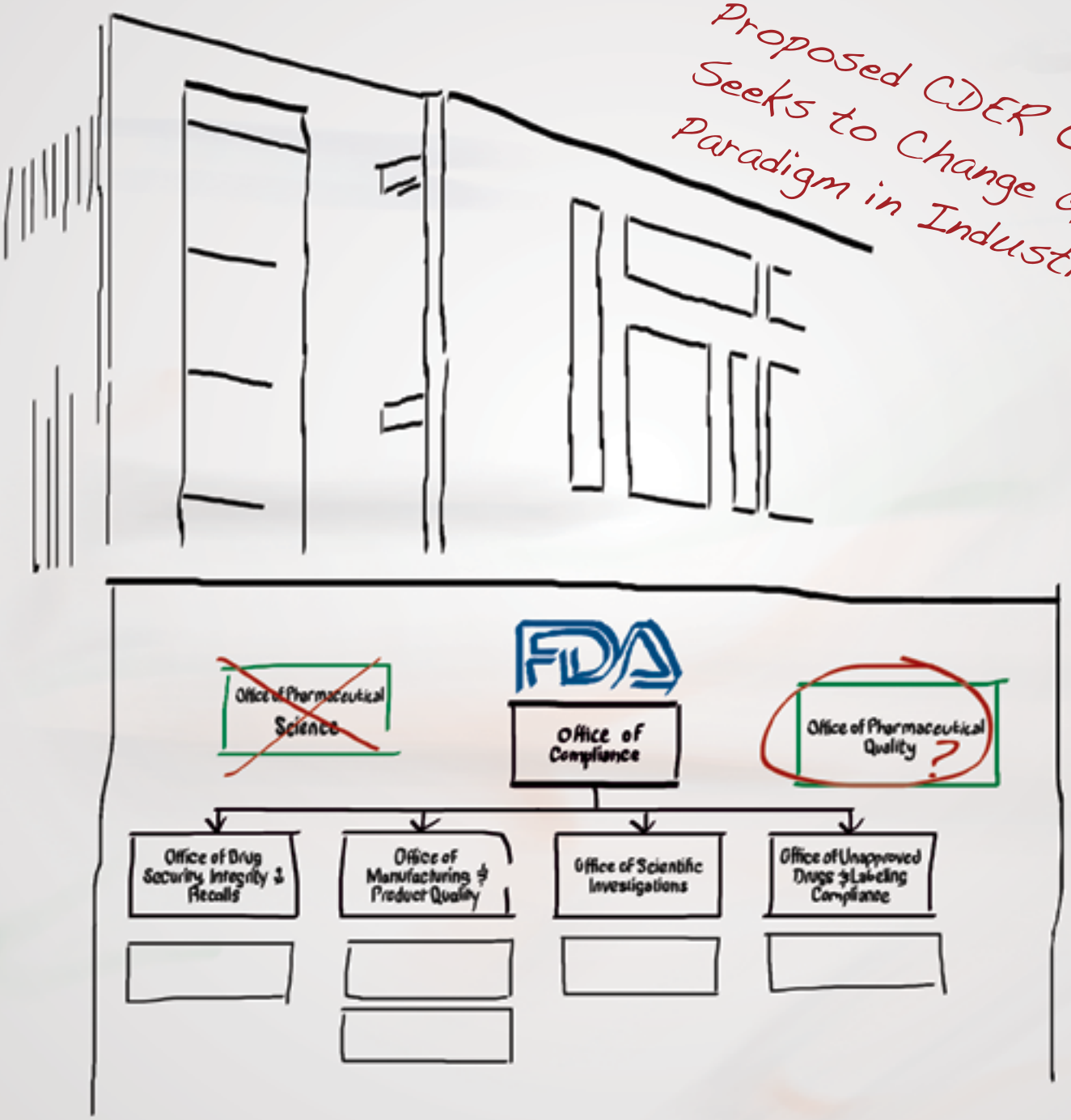

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PDA Parenteral Drug Association

The Parenteral Drug Association presents...

2013 PDA ANNUAL MEETING

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

April 15-17, 2013

The Peabody Orlando | Orlando, Florida

Conference Agenda Now Available Online!

The *2013 PDA Annual Meeting* is the meeting place this April. The distinguished Program Planning Committee is hard at work to bring you ***the best*** content in the industry. They know what you are concerned about, what you want to hear and who you want to hear it from.

The Best Content in the Industry

Conference Highlights Include:

- **Focus on three key tracks:**
  - Biological Sciences
  - Sterile Product Manufacturing
  - Quality Systems
- **Opening Plenary Sessions** on advances in therapy, uses of products, industry trends and much more. There will be a presentation from a patients perspective by Joyce Bloomfield, Executive Director, Global GMP Systems & Compliance, *Merck Sharp & Dohme*
- **Plenary Session Two:**
  - **Drug Shortages,** Marty Nealey, Vice President, Operations, Plant Manager, *Hospira Pharmaceuticals, Inc.*
  - **Counterfeiting,** Martin VanTrieste, Senior Vice President, Quality, *Amgen, Inc.*
- **Closing Plenary: The Future of Personalized Medicine**
  - **T-Cell Immunotherapy to Cure Cancer,** Carl June, MD, Program Director, Translation Research, Professor, Department of Pathology & Laboratory Medicine, *University of Pennsylvania Abramson Cancer Center*
- Poster Presentations
- Networking Receptions & Events like the 7th Annual PDA Golf Tournament at the Shingle Creek Golf Club & the PDA 7th Annual Walk/Run
- Post-Conference Workshop: PDA Human Factors Workshop on April 17-18
- PDA's Training and Research Institute (PDA TRI) will be offering six courses on April 18-19
- **Hotel located in the heart of Orlando's theme parks and area attractions – activities for the entire family!**

www.pda.org/annual2013

Exhibition: April 15-16 | Post-Conference Workshop: April 17-18 | Course: April 18-19

PDA Letter

Volume XLIX • Issue 1 www.pda.org/pdaletter

Cover

Proposed CDER Office Seeks to Change Quality Paradigm in Industry

Many industries set high standards for quality and base their branding on achieving high quality goals. This is most notable in the automobile industry, where carmakers such as Toyota (the Toyota Way) and Ford (Quality is Job 1) made it their corporate missions to promote the quality of their vehicles. And when quality defects impact their products (failing tires for Ford; unintended acceleration/brake problems for Toyota), the companies' sales take a big hit.

Cover Art Illustrated by Katja Yount

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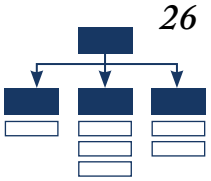


New CDER Office Seeks Improved Pharma Supply Chain

It has been 18 months since the U.S. FDA reorganized CDER's Office of Compliance, designating it as a "Super Office" and creating a number of new "Offices" within it: Office of Drug Security, Integrity, and Recalls (ODSIR), Office of Manufacturing and Product Quality (originally the Division of Manufacturing and Product Quality), Office of Scientific Investigations, and the Office of Unapproved Drugs and Labeling Compliance.

Microbiologists Key in Preventing Contamination

"If you see something, say something" has been the mantra of numerous homeland security agencies across the country and worldwide for over a decade. While aimed mostly at commuters, this message can also be applied to the microbiologists diligently working to identify microbial contaminants in the pharmaceutical industry.

PDA Survey: Business Case for Pharmaceutical Quality

This 2011 PDA benchmarking survey explores the business case for pharmaceutical quality by examining the cost of poor quality and the essential role of good quality systems in the pharmaceutical industry. The survey was open to the membership of PDA, ISPE and several other industry associations. Over 60 respondents participated in the survey representing companies of all sizes and manufacturers of various product types. The book is available at no charge.

Included in this 56-page book are the answers to 95 questions that paint a picture of how quality is supported throughout a respondent's company. The questions are broken into seven general categories: General Company Information, General Facility, Quality Organization, Quality Tools, Quality Metrics, Quality System and Quality Regulation.

A three-page introduction, which includes an extensive list of conclusions and opportunities derived from the survey results. The PDA Task Force that developed the questions and analyzed the results includes officials from the U.S. FDA, large bio/pharmaceutical companies, and well-respected consulting firms.

PDA Business Case For Pharmaceutical Quality Task Force Members

Joyce Bloomfield, Merck and Co.
Dave Chesney, PAREXEL Consulting
Richard Friedman, U.S. FDA
Francis Godwin, U.S. FDA
Nigel Hamilton, Sanofi
Jeffrey Hartry, PharmEng
Karthik Iyer, U.S. FDA
Richard Levy, PhD, PDA
Steve Mendivil, AMGEN
Claudio Pincus, Quantic Group, Ltd.
G.K. Raju, PhD, Light Pharma
Mahesh Ramanadham, PharmD, U.S. FDA
Susan Schniepp, Allergy Laboratories
Anders Vinther, PhD, Genentech
Glenn Wright, Eli Lilly and Co.

tinyurl.com/PDASurvey-BusinessCasePQ

The Parenteral Drug Association presents the...

2013 PDA Human Factors and Human Error Reduction Workshop

April 17-18, 2013

Peabody Hotel | Orlando, Florida

Despite advances in automation, pharmaceutical operations continue to involve the human – machine interface. As many internal investigations point out, human error continues to be a major causative factor. The challenge in advancing pharmaceutical operations is to reduce the potential for errors.

This workshop will present different quality systems tools that may allow managing improvements in operations as process re-design may be an outcome of an investigation taking human factors under consideration.

Visit **www.pda.org/humanfactors2013** for more information and to register.

The Parenteral Drug Association presents the...

2013 PDA/FDA Glass Packaging Conference

May 15-16, 2013 | Washington, D.C.

Exhibit space is available for this show. Contact Dave Hall at hall@pda.org to reserve your space today!

Pharmaceutical manufacturers, regulators, and glass suppliers all share a common goal of assuring the highest quality products (including packaging) for patients. The *2013 PDA/FDA Glass Packaging Conference* will provide information on integration of proteins with surfaces, an update on delamination issues and discuss key information trends.

This meeting will also further discuss best practices to preventing and/or detecting at-risk glass packaging and review current expectations to ensure that recalls are avoided and container closure integrity is assured.

PDA's Training and Research Institute will be hosting a training course following the *2013 PDA/FDA Glass Quality Conference*.

www.pda.org/glass2013

Conference: May 15-16 | Exhibition: May 15-16 | Course: May 17

PDA Volunteer Spotlight

Anil Sawant, PhD

- Vice President, Compliance
- *Johnson & Johnson Consumer Companies, Inc.*
- Member Since | **1992**
- Current City | **Skillman, NJ**
- Originally From | **Pune, India**

The best advice I ever received is you have a lot to learn; learn one new thing every day!

What are five of the most played artists on your iPod?

Eagles, Rehman, Pink Floyd, Michael Jackson, Adele

What is on your desk right now?

On my work desk…FDASIA documents, CPMG, org charts, budget report, travel receipts, to–do list. My home office desk… insurance claim forms, instructions on how to change the light engine of a DLP TV, and two non-functioning laptops with half the parts out from one.

If you weren't doing this job, what would you have done?

I would have done research in psychology.

Do you have any goals for 2013? A New Year's Resolution?

Mentor alumni and exercise regularly

What about the pharmaceutical industry keeps you up at night?

Another Black Swan event like the Tribromoanisole taint of products. Market forces are creating complex supply chains that are vulnerable to rare events with exponentially amplified risk of disrupting supply.

Can you give members insight on the time commitment and how your experience has been working on the PDA TBA Task Force?

I maintain a very busy schedule and time is a valuable commodity. Having said that, working on the TBA Task Force was one of the most satisfying professional experiences I have had. We had an excellent team of dedicated individuals who helped distribute the workload. They say change of work is play, and when you are having fun you don't keep track of time! Although I scheduled an hour a week, some weeks I spent more than that since I was having fun doing something different.

How has PDA benefited you professionally?

PDA helped me transition from academia to industry. It helped me build a network that I could tap into to benchmark, to learn. I still remember my first PDA conference and the experts I met. It was a conference on terminal sterilization in the early '90s.

Anil's specialty is primarily microbiology

NE Chapter Celebrates 2012 Aboard *Spirit of Boston*

Laurie Masiello, President and CEO, Masy Systems

With elections in November, the New England PDA Chapter celebrated the end of the chapter's year with a dinner cruise Sept. 19 in Boston Harbor on board the *Spirit of Boston.* About 80 members enjoyed beautiful weather and a bountiful buffet, while also appreciating the camaraderie of industry friends.

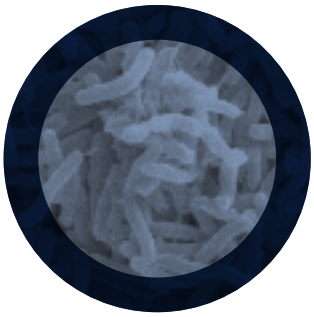
Meeting sponsors were hampered with short ceilings and the potential of rough seas. Instead of a traditional sponsorship with a table top display, sponsors brought varied raffle prizes which were real crowd pleasers.

Meeting managers **Rusty Morrison,** NE PDA President and Director, Process and Technology Services, Commissioning Agents, Inc., and **Laurie Masiello,** President and CEO, Masy Systems, invited sponsors to draw the winning tickets and present the prizes. The two top prizes, an iPad 2, donated by Commissioning Agents, was won by **Mark Maurice,** Sr. Project Manager, Sensitech; and two Bruins tickets, donated by Toxikon, were won by **Austin Caudle** of NSF. Other prizes were donated by Advantar Labs, BioVigilant, Charles River Labs, Complya, Masy Systems, Microtest Labs and World Courier.

(l-r) Mark Maurice, Sensitech (prize winner), Tulsa Scott, Commissioning Agents (donated iPad 2), Laurie Masiello, Masy Systems

(l-r) Austin Caudle, NSF (prize winner), Curtis Shondelmeyer, Toxikon (donated Bruins tickets), Rusty Morrison, Commissioning Agents

PDA's 7th Annual Global Conference on Pharmaceutical Microbiology



Last October, microbiologists from all aspects of the pharmaceutical industry converged on Bethesda, Md. to discuss hot button issues at PDA's *7th Annual Global Conference on Pharmaceutical Microbiology*. Topics of discussion included microbial contamination of product, biofilms, pyrogen and endotoxin testing, control of raw materials, package integrity, and much, much more! Additionally, mid-level managers provided tips for the field's "Future Leaders" and regulators provided updates on key regulatory concerns. All in all, attendees left the conference empowered by the important role played by microbiologists.

Opening Keynote Address

(l-r) Edward Tidswell, PhD, Baxter Healthcare Corporation; Matthew Arduino, CDC; Marla Stevens-Riley, PhD, U.S. FDA

Conference attendees chat with one of the exhibitors inside the Exhibit Hall.

Regulatory Updates

(l-r) Renee Blosser, U.S. FDA; Richard Friedman, U.S. FDA

Control of Microbial Contamination in Raw Materials, Components, and Bulk Solutions

(l-r) Anthony Cundell, PhD, USP General Chapters-Microbiology Expert Committee; John Metcalfe, PhD, U.S. FDA; Janet Perez Brown, Bristol Myers Squibb; Osama Elrashidy, Bayer Healthcare

Control of Product Package Integrity and Seal Quality

(l-r) Marla Stevens-Riley, PhD, U.S. FDA; Edward Smith, PhD, Packaging Sciences Resources; Dana Guazzo, PhD, RxPax; Ken Muhvich, PhD, Micro-Reliance

Control and Testing Strategies for Pyrogens & Endotoxins in Products and Processes

(l-r) Edward Tidswell, PhD, Baxter Healthcare Corporation; Clifford Holmes, PhD, Baxter Healthcare; Christian Supina, Baxter Healthcare; Thuy Bui, Pfizer, Inc.

Advances in Microbiological Control During Pharmaceutical Manufacturing

(l-r) John Metcalfe, PhD, U.S. FDA, James Rickloff, Sterilization Technology Group; Noe Miyashita, Hitachi; Claudio Denoya, PhD, Pall Corporation

Ask the Regulators – Expert Panel

(l-r) Marla Stevens-Riley, PhD, U.S. FDA; Julie Bailey, PhD; U.S. FDA; Cynthia Jim, U.S. FDA; Rebeca Rodriguez, U.S. FDA

Key Challenges in Microbial Control of Biopharmaceuticals

(l-r) Amy McDaniel, PhD, Pfizer, Inc.; Ruth Daniels, PhD, Genzyme; Brandye Michaels, PhD, Pfizer, Inc.; Kalavati Surna, PhD, U.S. FDA

Preparing the QC Micro Workforce of the Future

(l-r) Ed Balkovic, PhD, Genzyme; Neal Machtiger, PhD, Microbiology Solutions; Dona Reber, Pfizer, Inc.; Patrick Spain, Genzyme

Future Leaders

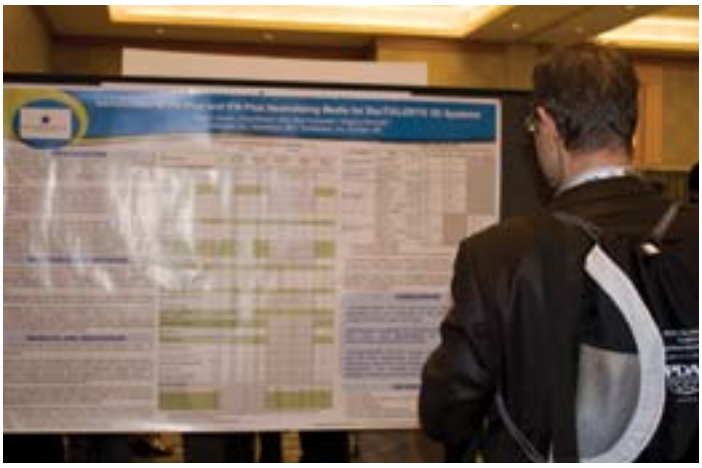
(back) Kevin Luongo, Shire Human Genetic Therapies

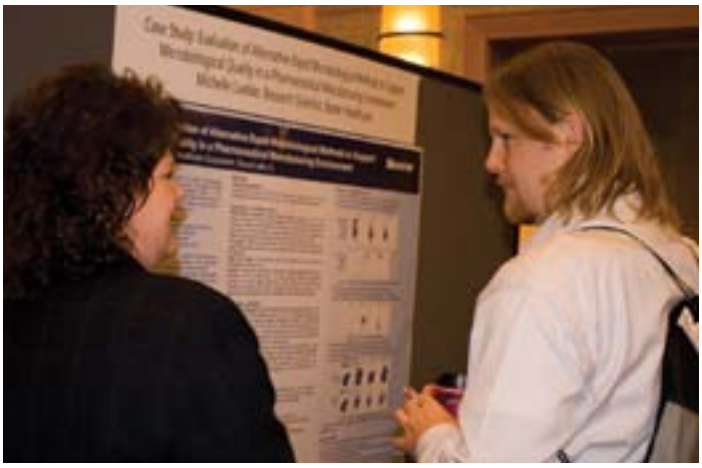
(top l-r) Julie Barlasov, Perritt Laboratories; Sophia Asefi, Bayer Healthcare, Inc.; Osama Elrashidy, Bayer Healthcare, Inc.

(bottom l-r) Devon Kleindienst, Bristol-Myers Squibb Company, Ebony Arrington, Pfizer, Inc.; Jacqueline Hansen, PhD; Associates of Cape Cod, Inc.

Exhibitors Hall

Poster Exhibits

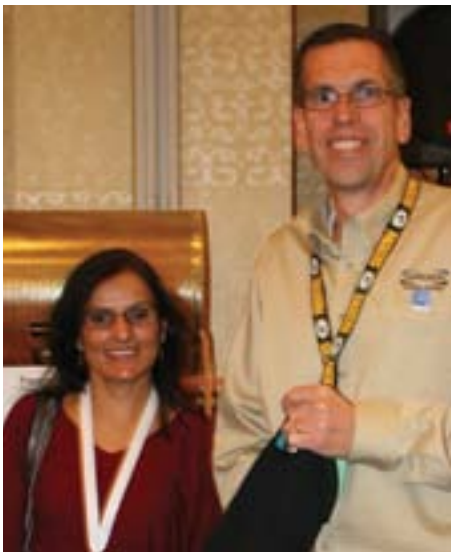




Passport Raffel

Nandini Bhattachavya collects a prize from Lancaster Laboratories

Jagruti Sharma won a prize from Veltek



Parul Daphtary won the drawing from Walker Barrier

Robyn Wanoz wins a Kindle from Microbiologics

Kendral Smith takes home an iPod from Associates of Cape Cod

Tech Trends continued from page 17

were left outside for about a week. English provided results specifically for the pallet covered with white, corrugated fiberboard. Here, there were numerous spikes in temperature yet beneath the cover it was about 12 degrees cooler during those spikes in temperature.

In another experiment, this time in Puerto Rico (the previous experiment took place in Europe), a reflective pallet cover was compared to a non-reflective cover. Temperatures under the reflective pallet cover were much lower (48 degrees Celsius) than temperatures under the non-reflective cover (70 degrees Celsius).

One thing to consider, however, is that while stretch films and foil covers are effective at reflecting energy they also trap moisture. This presents an issue potentially for affecting fiberboard packaging and damaging the product. Options to prevent moisture include Tyvek and other breathable covers.

While pallet covers are an option, English emphasized that they only offer protection from direct sunlight not ambient temperatures.

But could a box alone maintain the temperature of a shipment? English tested a brown box, a white box, and a box composed of metalized, reflective material. This experiment suggested that the white box and the metalized box provide better protection than the brown box.

For manufacturers concerned about ambient temperatures, English suggested insulated shipping containers. Depending on the needs of the shipment, there are active and passive containers. There are also shipping containers that use refrigerants.

Another option would be to explore special services offered by other companies that include expedited handling to prevent lengthy exposure to ambient temperatures and third party application of pallet covers or insulated containers.

As far as which specific solutions he recommends, English urged attendees to consider the needs of the company. While his company uses insulated containers, this might not be cost-effective for a small manufacturer. In the end, a manufacturer needs to fully understand the products as well as what shipping lanes will be used to determine the appropriate options for thermal protection.

About the Expert

Michael English has worked in the pharmaceutical industry for more than 23 years. Beginning with a position in Quality and moving to positions in Planning, Logistics, and Continuous Improvement, Michael landed in Packaging Technology where he has spent the last 12 years on Cold Chain packaging and shipping issues. Michael currently has responsibilities for not only qualifying new shipping systems but also for driving cold chain policy throughout the Merck network.

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Micromanaging vs. Coaching

Nathan Jamail

One of the greatest misunderstandings in leadership and coaching is the term "micromanaging". Most leaders never want to be thought of as a micro manager. In fact, it could be considered an insult or weakness of any manager. When micromanaging is used as a coaching or leadership style it will most likely deliver bad results, stifle creativity, limit employees' self-worth and without a doubt limit productivity. On the other hand when a coach or leader must deal with a bad performer it is imperative to help the employee either become a better performer or help them find a job that is a better fit. Leaders should strive to be a coach who when necessary, uses micromanaging *activities* to improve specific areas, but uses coaching *skills* when getting the team ready to *win*.

Why Micromanaging And Coaching Are Often Confused

Micromanaging and coaching are often confused because from the surface, the activities and the leader's involvement look very similar. The key difference is the leader's *intent* and desired goals of their action. Both require the involvement of the leader; setting clear expectations, well-defined activity management, accountability and a huge time commitment from the leader *as well as* the employees. The difference lies in the *purpose* of these activities. For example: a leader is setting expectations to ensure there is complete understanding of what they expect from each employee in order to maximize productivity and limit confusion:

- A micromanager does this with the intent to set boundaries and rules. A coach shows his commitment to the team by holding *everyone* accountable.
- A micromanager uses accountability to ensure the employee is earning their paycheck (oftentimes focusing on single employees versus the team). A coach manages activities to ensure the employees are on the right track and that they are in the best position to succeed.
- A micromanager uses the activities to justify effort or discipline. The micromanaging method is proved wrong when a *coach* understands it is not the amount of time an employee contributes as much as it is the focus and effectiveness of the time they contribute. The intent of coaching is to develop and prepare the employees to succeed using the leader's knowledge and experience to guide the employees, not to justify actions.

Action item: Don't be afraid of being a coach because you don't want to micromanage. Get involved and share the intent of your actions with your team so they understand your goals for not only yourself, but for *them- which ultimately is the goal for success.*

Every Great Coach Must Use Micromanaging Tactics

As stated, the main issue with leaders and managers is they misunderstand what "micromanaging" is and is not. Micromanaging is a tactic of coaching (or should be); it is not a leadership style. Micromanaging should be used as a *consequence* for those employees that are not meeting expectations or are bad performers. A bad performer does not necessarily mean a bad employee. There are many employees that are not performing well because they are in the wrong job, not because they are bad people, or they are not doing what they are passionate about in general, thus have no desire to be successful. By micromanaging the details of such an employee it allows the leader and the employee to make the best decision of what action should be taken next.

When To Micromanage and How Long

Let's say there is an employee who appears to be unhappy and their activity and results are not meeting expectations. The leader should get involved early to determine if the shortcoming is a lack of desire or ability, or both. To help determine the issue, the leader should implement more disciplined expectations and activities and *explain* to the employee why this action is being taken as well as the desired outcome. The desired outcome should be to either help the employee reach the expected activities, attitude and results or help them find a role that is a better fit. These micromanaging activities should be *short-term* activities.

The leader needs to make assessments quickly and take on the continued shortcomings, which results in moving the employee out of the position. In turn, the leaders should also take quick action to recognize great efforts and achievements as warranted. A leader should not have to im-

plement a micromanaging activity for an employee for more than 90 days and can be stopped in as little as 30 days depending on the level of involvement, improvement and accountability, as well as overall attitude and commitment of the employee.

Action item: Micromanaging is a tactic, not a style. When you have a poor performing employee, implement a performance plan of daily and weekly activities and micromanage those activities to help them move up in performance or out of the position that does not fit them. You owe it to them as their leader and coach.

Why Most Leaders Don't Like To Coach

All leaders, or at the least the majority of leaders, prefer to avoid confrontation. This is unfortunate as only in *constructive* confrontations and discussions can progress be made. It is all in the *intent* of the confrontation. If the intent is to just belittle, or point out all the obvious issues with an employee, then yes that is a destructive and useless conversation and understandable as to why one would want to avoid it. However, in order to be an effective coach, a leader must approach confrontation with the intent of *helping* the employee.

It is absolutely impossible to coach without confrontation and discussion regarding areas of opportunity. When an employee is confronted by a leader who expresses the desire to help them achieve success, points out areas of opportunity for improvement and suggests a game plan to help them achieve such improvement, the confrontation just took the route of establishing a plan for success. It is a win-win for both parties. Of course at this point it is up to the employee to demonstrate their desire for success and jump on board, but it is also the leader's job to micromanage through the issues until a satisfactory ending is in sight. Is this hard to do? It is, only if the intent is wrong. Is it necessary? Absolutely.

Final Thought

Not every hire is the right hire and not every job is the right job, but accepting either one just because it is easier is wrong. Micromanage through the issues by helping your employees either become great at what they do, or helping them to find something they will be great at. Outside of issues with poor performing employees, your job as a leader is to *coach* your entire team to success.

About the Author

Nathan Jamail, president of the Jamail Development Group and author of "The Sales Leaders Playbook," is a motivational speaker, entrepreneur and corporate coach. As a former Executive Director for Sprint, and business owner of several small businesses, Nathan travels the country helping individuals and organizations achieve maximum success. His clients include US Army Reserves, Nationwide Insurance, Metro PCS, State Farm Insurance, Century 21, Jackson National Insurance Company and ThyssenKrupp Elevators. To book Nathan, visit www.NathanJamail.com or contact 972-377-0030.

snapshot

PDA Publishing Activities up in 2012; TR Portal Introduced

Walter Morris, PDA

PDA stepped up its publishing activities in 2012 by launching a new series called "PDA Proceedings" and issuing our second "PDA Survey."

The new proceedings category offers those who miss certain PDA conferences a chance to purchase a full transcript and the slide presentations. PDA will carefully select meetings based on the technical merit of the proceedings and the interest among our members and intends to publish two per year. In 2012, the meetings chosen were the *PDA/FDA Virus and TSE Safety Conference* and the *2012 PDA Innovation and Best Practices on Sterile Technology Conference.* PDA also plans to make these available in hardcopy for interested readers.

These transcripts of the proceedings are prepared by an experienced transcription service. PDA's publishing team carefully placed the slides with the transcripts so that readers can reference the slides as they read. Most presentations and Q&A sessions are included.

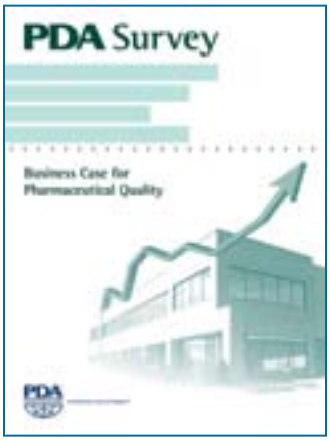
PDA also published its second in its new collection of industry surveys. The *2012 PDA Survey: Business Case for Pharmaceutical Quality* was a work-product of a joint PDA and U.S. FDA Task Force and published in December. For more information, turn to the article in News & Notes in this issue (page 6).

In addition, PDA's continuing partnership with DHI resulted in four new titles in 2012.

Thanks in part to the new procedure for technical reports, which PDA Sr. VP **Richard Levy** discussed in this space in the Nov/Dec *PDA Letter,* the Association published eight technical reports in 2012. The last two published were TRs 59 and 29 (Revised).

Perhaps the biggest publishing event of the year was the launch of the PDA Technical Report Portal, which went live in December. The portal allows all Standard, Government and Honorary PDA members to view all active Technical Reports online. This new member benefit truly enhances the PDA experience!

All of PDA's publications can be found at the PDA Bookstore: www.pda.org/bookstore. Visit this website in 2013 to find our new releases throughout the year.



trarchive.pda.org/t/26426

To purchase any of these products go to www.pda.org/bookstore

Interest Group *Corner*

Cold Chain IG Explores Use of Thermal Blankets

Rebecca Stauffer, PDA

The Pharmaceutical Cold Chain Interest Group (PCCIG) met on a cold November morning during the *2012 Pharmaceutical Cold Chain & Good Distribution Practice Conference* sponsored by PDA. Interest group leader **Rafik Bishara,** PhD, touched on some of the group's recent efforts, including *PDA Technical Report No. 58, Risk Management for Temperature-Controlled Distribution*, published in September.

As a special treat for attendees of this interest group meeting, **Karl Kussow,** Manager of Quality and Validation, FedEx Custom Critical, provided an overview of best practice considerations for using thermal blankets, including examples from services that FedEx Express and FedEx Custom Critical offer to protect certain sensitive shipments for transportation by air. **Jean Pierre Emond,** PhD, Director of Cold Chain Research, Georgia Tech Research Institute, then offered a scientific perspective supporting the use of thermal blankets in shipping.

"The strategy for thermal blankets is very similar to what you're already used to doing for all of your cold chain," said Kussow as he opened his presentation by honing in on strategy. He also noted that as air affects the temperatures during cold chain storage and transportation, "then process becomes very important."

If a company chooses to use thermal blankets, Kussow recommends keeping two objectives in mind: utilizing the blankets to protect cargo from spikes in temperature and to control the effect of ambient temperature around the cargo during transit.

Next, he illustrated the use of thermal blankets during a shipment from India to the United States. The shipment reached a transfer point in Dubai; this stage of the cold chain was of great concern to the company. Kussow provided data showing that there were extremely high temperatures during the time the shipment was in Dubai. External temperatures approached 45 degrees Celsius.

Through the use of monitors underneath the blanket as well as on top and on the sides of the container, the company determined that the blanket delayed the effects of the extreme heat on the product by several hours. This delay, combined with appropriate process to limit the time exposed to the extreme heat, resulted in achieving the temperature objectives for that shipment.

Kussow then addressed the effectiveness of thermal blankets based on observations.

"They've been effective when combined with effective systems and process control, to economically protect products despite sometimes wide variations in temperature as they are trans-

Continued on page 18

Tech *Trends*

Options Abound for Shipping Cold Chain Product

Rebecca Stauffer, PDA

It's a well-known fact that temperatures can fluctuate throughout the process of shipping products across the globe by air. Freight is left out on the tarmac in desert temperatures while temperatures can get close to freezing within the cargo hold of an aircraft. This might not be a concern for manufacturers of clothing or toys, but for pharmaceutical manufacturers shipping room temperature products it is a prime concern.

For this reason, **Michael English**, Associate Director, Engineering, Merck & Co. Inc., provided attendees at the last plenary session of the *2012 Pharmaceutical Cold Chain & Good Distribution Practice Conference* an overview of various thermal protection options for shipping room temperature products.

"Why do we need any kind of temperature protection? Well, of course this is too maintain the quality of our products," he said. "We know that both cold and heat affect the products."

He provided examples of how temperatures can affect certain products from liquid solutions undergoing phase changes due to cold temperatures to degradates forming due to excessive heat. Packaging can also be affected by heat as well as moisture.

So how can a manufacturer protect room temperature product?

"One, you have to know your product," said English. While a product may have a specific storage temperature, a manufacturer also needs to know the shipping temperature allowance.

Cargo shipped via air carries its own concerns, notably the issue of exposure to sun while on the tarmac during transit. English emphasized that the standard operating process involves shipments being towed to the tarmac five or six hours before departure. In the course of this process, while ambient temperatures might be in a decent range, exposure to sunlight could have a significant impact on the product.

"The vast majority of our temperature excursions during air shipments of consolidated freight have been at the airport pending loading on the aircraft," said English.

So what options are there for companies to protect temperature sensitive cargo during these times?

English listed a variety of options for protecting cargo. Pallet covers are one such option. These are available in a variety of materials, including opaque, white stretch wrap, foil layered over air bubbles or foam, a white breathable membrane such as Tyvek, and white, corrugated fiberboard. Ultimately, pallet covers reflect sunlight.

To determine the levels of protection offered by various pallet covers, English tested a variety of pallet covers. These covers included foil with black trim on the bottom, foil with white velcro straps, double foil with bubbles, straight foil, white, corrugated fiberboard, and regular stretch wrap. These pallets

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ported through various seasons, continents, weather, and facility conditions," he said, citing a shipment where product was exposed to extremely cold temperatures during a stop in transit yet the product stayed above 10 degrees Celsius.

Ultimately, Kussow views the use of thermal blankets as being part of a holistic system that integrates the capability of the blanket, the transport system, and procedural controls to safeguard cargo from fluctuations in temperature.

Kussow views the use of thermal blankets as being part of a holistic system

Emond then provided a more academic viewpoint of thermal blankets, beginning with some background concerning sources of heat.

"We have different [ways] of getting the heat from something," he said. "We can have radiation from the sun, radiation from the ground, convection from air movement and we can have conduction from the ground or surface."

He reminded listeners that heat is moving and not the cold. As a scientist by training, he wanted to explore the effects of solar radiation on a pallet laying out on the tarmac. He studied three different methods of protection—regular stretch-wrapped padding, dense materials like those used for sleeping bags, and Tyvek.

The pallets were then left outside on a clear day with temperatures approximately 20 degrees Celsius. Although relatively mild, the pallet with the regular padding had a surface temperature much higher at about 56 degrees Celsius. The one wrapped in dense material had a surface temperature of 58 degrees Celsius and the Tyvek covered pallet's surface temperature was 22 degrees Celsius—much closer to the outside temperature.

This experiment illustrated the importance, Emond emphasized, of making solar radiation a critical point of consideration during shipping. Additionally, manufacturers should also look into the effects of ground radiation and other factors when determining what type of product to use for cold chain product.

"You have to fight things," he said. "And you have to understand what you're fighting for."

After both Kussow's and Emond's presentations, Bishara spoke about the hard work of the PCCIG's steering committee. He explained that the committee includes members from many facets of the cold chain industry except in the area of security. This means he may reach out among interest group members to invite someone to join the committee with a background in security. He's especially interested in members who've made it a point to be heavily involved in the group and take on a number of projects related to cold chain, such as work on Technical Reports, involvement with conferences, and task force leadership.

About the Experts

Rafik Bishara, PhD, has become one of the most respected figures in the pharmaceutical cold chain distribution sector, following a distinguished 35 year career with Eli Lilly & Co. as Director, Quality Knowledge Management and Technical Support. He is a Temporary Adviser to the World Health Organization (WHO) since July 2007. He has been acting as mentor and training adviser to the WHO/PDA "Pharmaceutical Cold Chain Management on Wheels." Dr. Bishara is a member of the Editorial Advisory Board of Pharmaceutical Outsourcing Journal; Life science Leader Magazine; and the Board of Advisors of BioConvergence, LLC, and MARKEN LLP.

Jean Pierre Emond, PhD, is the director of Cold Chain Research in the Electro-Optical Systems Laboratory at Georgia Tech Research Institute. He is also currently the COO at The Illuminate Group, a company offering consulting and customized cold chain solutions.

Karl Kussow is the Manager of Quality and Validation for FedEx Custom Critical. Kussow leads the company's efforts to supply its customers with temperature-controlled shipping services and quality management assistance. logistics experience in operations, safety, regulatory compliance and quality assurance.

PDA Recognized By *BioProcess International*

Rebecca Stauffer, PDA

BioProcess International recently recognized PDA as a finalist for the publication's 2012 international awards in upstream processing, downstream processing, and manufacturing in the category of Collaboration of the Decade. The judges selected PDA as a finalist in manufacturing Collaboration of the Decade for facilitating communication and collaboration between industry and regulators. Ultimately, finalists for the Collaboration of the Decade award are recognized for "innovative partnerships" that seek to transform the industry.

PDA's Sr. VP of Scientific and Regulatory Affairs **Rich Levy,** PhD, attended the award dinner and ceremony which was also held during the BioProcess International Conference.

BioProcess International also recognized PDA members **Jim Akers,** PhD, President, Akers Kennedy & Associates, **Jerold Martin,** Sr. VP, Global Scientific Affairs, Pall Corporation, and **Duncan Low,** PhD, Scientific Executive Director, Amgen as finalists in Thought Leader of the Decade. Akers was a finalist for the award in the manufacturing pillar while Low was a finalist in the category of downstream processing. Jerold Martin was a finalist in both categories as well as upstream processing. Ultimately, Martin received the Thought Leader of the Decade award in manufacturing for his work in driving a paradigm shift in the area of biomanufacturing.

(l-r) Nicole Brockway, AVP, Market Development, Life Technologies; Rich Levy, PhD, PDA

Companies that regularly exhibit at PDA conferences were also finalists, and in some cases winners, in a few categories. **Thermo Scientific** was a finalist in the category of upstream processing Technology of the Decade for its first commercially available single use, stirred tank cell culture bioreactor. **Sartorius Stedim Biotech** was one of the winners of the upstream processing Collaboration of the Decade award for its work with **Refine Technology** and **GE Healthcare** on worldwide supply and distribution agreements in the development of novel filtration systems. Additionally, Sartorius was a finalist for the manufacturing Technology of the Decade for the innovative development of single-use applications.

Amgen was a finalist in the category of downstream processing Technical Application of the Decade due to its Computational Fluid Dynamics product. **Boehringer Ingelheim** was a finalist for downstream Collaboration of the Decade for its work with the **University of Applied Sciences Biberach, Rentschler Biotechnologie GmbH,** and the **Karlsruhe Institute of Technology** for work on creating GMP-compliant and reproducible robust crystallization methods. **Vetter Pharma International** was a finalist for manufacturing Technical Application of the Decade for developing clinical trial solutions for filing drug delivery systems.

And finally, **Merck** was one of the finalists for manufacturing Collaboration of the Decade for working with **MedImmune** on a trusted partner network.

Life Technologies, another regular PDA exhibitor also sponsored the Manufacturing pillar awards.

PDA wishes to thank its members in both industry and regulation for making this possible.

Proposed CDER Office Seeks to Change Quality Paradigm in Industry

Rebecca Stauffer, PDA

Many industries set high standards for quality and base their branding on achieving high quality goals. This is most notable in the automobile industry, where carmakers such as Toyota (the Toyota Way) and Ford (Quality is Job 1) made it their corporate missions to promote the quality of their vehicles. And when quality defects impact their products (failing tires for Ford; unintended acceleration/brake problems for Toyota), the companies' sales take a big hit.

Not so much in the pharmaceutical industry. People buy medicines, mostly prescribed by doctors, and rarely consider the quality. It is assumed that highly regulated drugmakers deliver products of the highest quality.

Yet, industry and regulatory observers have noted that for pharmaceutical manufacturers, quality has not achieved the prominence it has compared to other industries. The issue first came to a head in 2002 when the U.S. FDA launched *Pharmaceutical cGMPs for the 21st Century*, which later changed the name of the initiative to *Pharmaceutical Quality for the 21st Century* to reflect a more general focus of improving quality within the industry. Led by CDER Director, **Janet Woodcock,** MD, the initiative has been at the forefront of numerous quality-related movements including Quality by Design (QbD), Process Analytical Technologies (PAT), cGMP harmonization, ICH Q8, Q9, and Q11, and process validation.

Still, ten years after the launch of the initiative, the industry remains beleaguered by various quality problems that force recalls, cause regulatory actions, and worst, sink the company into a costly consent decree with FDA that results in plant closures or manufacturing suspensions—all of which endanger patients.

At a PDA/FDA workshop on ICH Q10 (held after the *2012 PDA/FDA Joint Regulatory Conference*), numerous experts from both industry and regulatory authorities spoke about quality's continued limited focus within pharma (See the November/December issue of the *PDA Letter,* p. 34). In the May-June 2012 edition of the *PDA Journal of Pharmaceutical Science and Technology*, Woodcock, referring to quality, said "We must ask ourselves, in an area where the stakes are so high, why is this not being achieved?"

Then in September, Woodcock announced a number proposed organizational changes at CDER, including development of a new Office of Pharmaceutical Quality (OPQ). This office, as envisioned, would be tasked with overseeing quality throughout the lifecycle of a drug product and take over some of the functions of the Office of Pharmaceutical Science (OPS). In her letter announcing the changes at CDER, she stated:

> "Quality is the underpinning of everything we do, and it is imperative that we have a drug quality program as robust as those programs we presently have for drug efficacy and drug safety. Further, we must be strategic and have systems in place to identify and respond to quality issues before they become problems. This is especially critical due to the global nature of drug manufacturing and the sourcing of raw materials outside of the United States."

Additionally, she proposed elevating the Office of Generic Drugs to a super office due to the passage of the Generic Drug User Fee Amendments of 2012 (GDUFA) as well as greater consumer focus on generic medications.

This follows a realignment within CDER that took place last year, resulting in the elevation of the Office of Compliance into super-office status as well as the development of the Office of Drug Security, Integrity & Recalls (ODSIR) (See story on p. 26).

But what does the possible establishment of an Office of Pharmaceutical Quality mean for the industry? The *PDA Letter* spoke with two members of the PDA Letter Regulatory Affairs and Quality Advisory Board—the body of member volunteers who regularly form PDA's opinions on new regulatory initiatives.

Sue Schniepp, VP, Quality and Regulatory Affairs, Allergy Laboratories, foresees a positive outcome for industry.

"I think it will have a good impact," said Schniepp. "It would be great to have an office within the FDA where you could go and explain your new technology and get some sort of scientific opinion approval to go ahead and move forward."

She then added "when you move forward and you put in these new technologies you want to be able to do it with a minimum amount of shutdown time...it would be great to have an office within CDER that focused on the scientific elements of some of these new technologies that would advance the industry and make it easier to actually file changes."

On the other hand, **Alan Burns,** VP, Global Quality, Sartorius, is concerned about the Agency's resources to build another office geared specifically for assuring quality in manufacturing.

"I think timing is everything, and I don't think this is a good time to do it," he said. "I don't see major issues out there, above the normal noise level that you normally see in the industry that would prompt this type of approach."

Burns believes the fungal meningitis outbreak caused by a careless compounding pharmacey is going to sap FDA resources. "From everything that I've read," he said, "It sure seems that there's going to be a lot of pressure on FDA to get more involved in the oversight of compounding pharmacies."

In fact, during the writing of this article, FDA Commissioner **Margaret Hamburg,** MD, recommended to Congress in a prepared statement before its hearing on the meningitis outbreak on November 14 that the Agency expand its oversight to include compounding pharmacies producing drugs on a large scale. Traditional compounders developing specialized medications for individual patients would be exempt.

Burns also pointed out that plans to expand the Office of Generic Drugs might also impact plans to develop an Office of Pharmaceutical Quality, and he worries that in a time of cost-cutting, the

Article at a Glance

- CDER Director Janet Woodcock proposes an Office of Pharmaceutical Quality
- Quality in manufacturing has been highlighted by media, regulators since early 2000s
- Experts differ on the effect of a potential new office on industry

Ten years after the launch of the initiative, the industry remains beleaguered by various quality issues

Agency might be stretching itself thin.

As far as how the recent meningitis outbreaks caused by sterile compounding will affect the Agency's push for greater quality in manufacturing, Schniepp thinks it could dilute efforts to establish quality due to the sheer number of compounding pharmacies across the United States. This will depend, of course, on whether or not oversight of compounding pharmacies will remain under individual states.

"So if it's going to remain as a state initiative, or state responsibility, somehow there has to be some sort of liaising with the FDA to make sure that the states know and understand what to audit for."

Schniepp also believes that quality remains an issue within pharma.

"I think you can see that as evidenced by a number of the 483s that have come out against well known players in the industry," she said. "So I think there's still an issue."

Burns agrees.

"I think quality is an issue and always will be an issue in the industry because of the nature of what the industry produces," he said. "I think it's well-documented that over time that if you turn your back too much on manufacturers that, you know, bad things can happen."

In lieu of developing a new office, he'd prefer to see the FDA leverage its existing resources. Pointing out that the Office of Pharmaceutical Quality would be overseeing product lifecycles, he noted that "those responsibilities are already there and they're just in different areas of FDA and in different offices."

"I just think this approach with creating a new office is the wrong way to go," he added. "I think if anything, they should beef up the surveillance methods that they already have by way of more frequent visits and more concentrated efforts in certain areas instead of trying to do this through the formation of a new office."

As one of the group leaders of PDA's Management on Outsourced Operations Interest Group, Schniepp thinks that if an Office of Pharmaceutical Quality is developed, it's purview should include contract manufacturing.

"I don't think everybody quite understands what goes on there," she said referring to the client/contract manufacturer relationship. "And I'm not sure there's a lot of regulation behind it, other than to say that contract manufacturers are an extension of the company that the client needs to understand what the contract manufacturer is doing. But there are a lot of different clients out there, some that understand the regulations and some that don't. And when you put together a client that doesn't understand the regulations with a contract manufacturer that doesn't understand the regulations you have a recipe for failure."

In the end, whether or not the Agency moves forward with creating the Office of Pharmaceutical Quality or just expands its existing resources, the issue of quality is not going away, especially since it has been a focus for Woodcock since the early 2000s. It is worth noting that the launch of the *Pharmaceutical Quality for the 21st Century* initiative followed a 2001 report by PricewaterhouseCoopers that illustrated the industry's high Cost of Quality. This was later echoed in a 2003 *Wall Street Journal* article noting that pharma manufacturing techniques lagged behind "potato chip and laundry soap makers." Ultimately, the goal of the initiative, according to Woodcock, was the establishment of "a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight."

In the end, time will tell if the Agency can spur a greater emphasis on quality within manufacturing. Perhaps one day, television viewers will see commercials for pharmaceutical products highlighting quality as opposed to just the mere effectiveness of the drug.

About the Experts

Alan Burns is Vice President of Global Quality for Sartorius, an international supplier of biopharmaceutical equipment and materials to the drug industry. He has held various quality positions in the drug industry for nearly twenty years, including stints with Abbott Laboratories, Bayer Healthcare, and Eli Lilly. Burns is a member of PDA's Regulatory Affairs and Quality Advisory Board, which he serves as North American liaison, and is also a member-elect of the Rx-360 Board of Directors.

Sue Schniepp is currently Vice President, Quality and Regulatory Affairs for Allergy Laboratories. 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.

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JANUARY EVENTS

15-16
Single Use Systems for Pharmaceutical Applications
Milan, Italy
https://europe.pda.org/SingleUse2013

FEBRUARY EVENTS

5-6
Modern Biopharmaceutical Manufacturing
Lyon, France
https://europe.pda.org/Biopharm2013

7
Freeze Drying of Vaccines Training Course
Lyon, France
https://europe.pda.org/TCBiopharma2013

11
Pre-Conference Workshop on VHP Decontamination
Ulm, Germany
https://europe.pda.org/WSParDrug2013

11-15
Aseptic Processing Training Program – Session 1 Week 1
(Week 2: March 4-8)
Bethesda, Maryland
http://www.pda.org/2013Aseptic

12-13
Parenteral Drug Development – Clinical Trial Materials
Ulm, Germany
https://europe.pda.org/ParDrug2013

26-27
Pharmaceutical Microbiology
Berlin, Germany
https://europe.pda.org/Microbio2013

28-1 March
The A to Z's of Biofilm Control, Monitoring, Validation, and Excursion Investigations of Pharmaceutical Water Systems Training Course
https://europe.pda.org/Biofilm2013

28-1 March
Microbiology – Rapid Microbiological Methods Training Course
Berlin, Germany
https://Europe.pda.org/TCRMM2013

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MARCH EVENTS

5-6
Parenteral Packaging
Prague, Czech Republic
https://europe.pda.org/ParPack2013

7
Container Closure Development Training Course
Prague, Czech Republic
https://europe.pda.org/TCCCD2013

7
Interest Group Meeting Pre-filled Syringes
Prague, Czech Republic
https://europe.pda.org/IGPrefilled2013

18-19
2013 PDA Analytical Methods Development & Validation Workshop
Baltimore, Maryland
www.pda.org/amd2013

18-22
Pharmaceutical Products Supply Chain Integrity: A Five Day Training Series
Bethesda, Maryland
www.pda.org/pharmaintegrity

19
Interest Group Meeting Visual Inspection
Berlin, Germany
https://europe.pda.org/IGVisInsp2013

20-21
An Introduction to Visual Inspection Training Course
Berlin, Germany
https://europe.pda.org/TCVisInsp2013

New CDER Office Seeks Improved Pharma Supply Chain

Rebecca Stauffer, PDA

It has been 18 months since the U.S. FDA reorganized CDER's Office of Compliance, designating it as a "Super Office" and creating a number of new "Offices" within it: Office of Drug Security, Integrity, and Recalls (ODSIR), Office of Manufacturing and Product Quality (originally the Division of Manufacturing and Product Quality), Office of Scientific Investigations, and the Office of Unapproved Drugs and Labeling Compliance.

As a super office, the Office of Compliance's role was designed to utilize the office's scientific, technical, and legal expertise "with closely related program areas, leveraging our resources and maximizing its ability to achieve its public health mission," according to a May 26, 2011 all hands memo from CDER Director **Janet Woodcock**, MD. The restructuring of the Office of Compliance became effective in June 2011. The goal of the restructuring was to address changes in the global pharmaceutical market.

These changes were announced and discussed with much fanfare at the *2011 PDA/FDA Joint Regulatory Conference*, yet since then, there has not been a lot of information from the Agency regarding what these new offices are doing. The *PDA Letter* has decided to find out how these new offices are functioning and what their key initiatives are. We start this issue with a look at ODSIR.

ODSIR was created in response to the globalization challenges of an ever-increasing pharmaceutical supply chain. At this time, ODSIR's role involves oversight of the security of the drug supply chain, counterfeit medications, recalls, adulteration, and import operations.

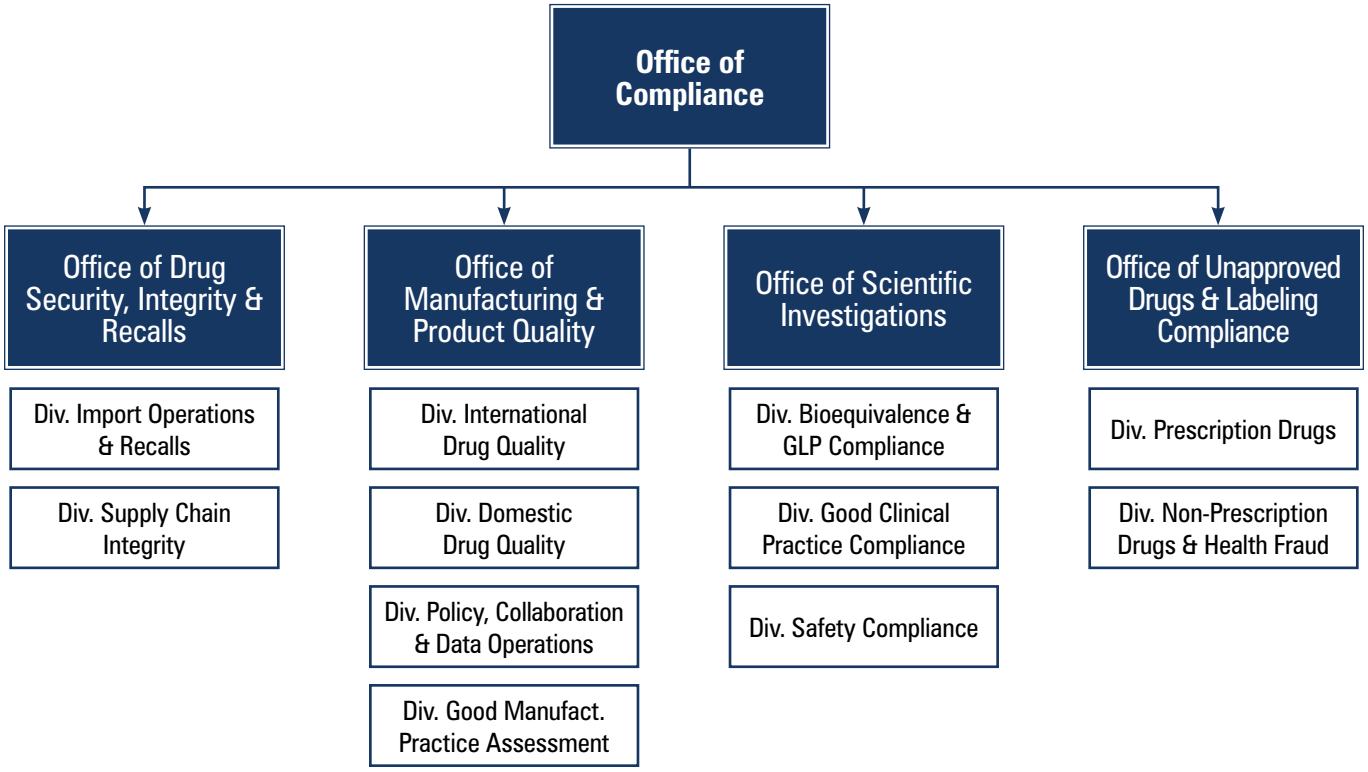
In the wake of additional restructuring at CDER proposed by Woodcock in September (See story on p. 20), the *PDA Letter* reached out to ODSIR for updates since the changes took place last year.

An ODSIR representative agreed to answer a few questions for the *PDA Letter.*

The representative said, "the establishment of ODSIR signals FDA's awareness of the challenges and risks associated with the increasing complexity of the global pharmaceutical supply chains. Recognizing that our current drug supply chain involves players that may be domestic or international, ODSIR is able to focus resources to better understand vulnerabilities of the supply chain from drug components to finished drug products, and to respond to threats to supply chain integrity that present risk to public health."

The representative also clarified ODSIR's structure. The office is split into two divisions--Import Operations and Recalls and Supply Chain Integrity. Within the Supply Chain Integrity division are three branches responsible for Import Policy, Finished Drug Security, and Drug Component Security. The Division of Supply Chain Integrity (DSCI) includes components originally found in other CDER divisions.

CDER Office of Compliance: Super Office Structure



"Bringing these groups together within ODSIR allows us to have dedicated staff for responding to and researching supply chain issues through enhanced communication and coordination necessary to address these complex issues," said the representative, adding, "due to ODSIR's mission to address the security of the entire supply chain, DSCI's work has been grouped into the identification of and addressing risks associated with both the components (excipients and APIs) and the finished drug product supply chains. The Import Policy Team works with closely with our Import and Exports Compliance Branch of our other division, working on import policy and online pharmacy issues."

The Division of Import Operations and Recalls consists of two branches: Recalls and Shortages and Import and Export Compliance. Both branches are responsible for handling import/export and recall issues with the other offices within the Office of Compliance: Office of Manufacturing and Product Quality, Office of Scientific Investigations, and the Office of Unapproved Drugs and Labeling Compliance.

"The Recalls and Shortages Branch evaluates and classifies drug recalls and coordinates recalls with our field offices and other parts of the Agency. They work closely with our Drug Shortage Program to assist in mitigating shortage situations," said the ODSIR representative. "The Import and Export Compliance Branch focuses on compliance issue related to imported and exported drugs and works closely with our field offices in the Office of Regulatory Affairs. This branch is responsible for reviewing and issuance of export certificates and developing policy and procedures related to import and export operations."

Another ODSIR mission involves, according to the FDA website, monitoring the "lifecycle of the product from drug components through to the finished dosage form delivered to the patient." The representative indicated that the office is exploring policy that would include the use of components, such as excipients, which have traditionally not been monitored.

"Our view of the supply chain includes the entire life cycle of the product from drug components through the finished drug, and the formation of ODSIR dedicates staff and resources to study and respond to drug supply chain issues," replied the representative.

In addition to answering questions for the *PDA Letter*, Lt. Commander **Thomas Christl**, Acting Director, ODSIR, spoke in November at the *2012 PDA/FDA Pharmaceutical Supply Chain Conference* in Bethesda, Md.

He provided an overview of ODSIR's mission and ongoing initiatives relating to supply chain security, particularly as the ODSIR representative stated that the office will

Office of Compliance Seeks Global Collaboration

Rebecca Stauffer

Along with Christl, **Ilisa Bernstein**, PharmD, Director, Office of Compliance, spoke at the *2012 PDA/FDA Pharmaceutical Supply Chain Conference*. In her presentation, Bernstein emphasized the role the Office of Compliance is taking as part of the Agency's plans to increase global cooperation and collaboration. These plans include: partnering with foreign counterpart agencies to develop global coalitions of regulations, building global information systems networks to facilitate the sharing of data, using risk analytics to enhance gathering of intelligence, and leveraging Agency resources based on risk using the combined efforts of government, industry, the public, and private third parties.

She noted that one of the big challenges her office faces "is how the supply chain has become so much more complex. There are so many more people, so many hands, so many countries that it's not just done all in one facility and one city anymore."

Her office is also one of several at CDER working to with overseas agencies to ensure the integrity of imported medications. Additionally, the FDA is also working with other federal agencies such as the Department of Homeland Security as well as global law enforcement entities like INTERPOL to identify gaps in the supply chain network.

"Global cooperation and collaboration is extremely important in this area," she said.

The office is exploring policy that would include the use of components, such as excipients

be working closely with the the Office of Regulatory Affairs and other Agency offices to implement the import provisions of the Food and Drug Safety and Innovation Act (FDASIA).

"As many of you are aware," Christl pointed out, "today's global [environment] makes things a bit challenging."

One initiative to alleviate some of these challenges is the development of a Track and Trace system. The Agency is working to develop a centralized database that tracks product throughout the supply chain cycle, beginning at packaging and ending at the pharmacy. The goals of this program are: preventing the introduction of drugs that are counterfeit, diverted, misbranded, or otherwise substandard, identifying substandard drugs, offering accountability as drugs move between supply chain participants, and to improve the efficiency of recalls.

Another initiative is through the Secure Supply Chain Pilot Program, a two-year pilot to determine if it's worthwhile and practical to create a secure supply chain program while accelerating entrance for specific imported drugs and APIs. Companies that want to participate must meet certain criteria to allow the Agency to determine if the drugs in question comply with FDA requirements. Ultimately, the goal of the program is to prevent drugs that do not comply with FDA guidelines from entering the country as well as expedite those drugs that do meet the qualifications into the United States.

"Generally, what we're looking to do here is work with companies who are interested in participating and setting these standards that they must meet in order to participate with the end goal or the benefit of having their products be able to move through the importation process quickly," he said.

Additionally, Christl highlighted Counterfeit Detection Device #3, or CD3, a handheld device unveiled by the FDA in September. This battery-operated LED device can be used to detect products that have been tampered with.

"It has been quite successful," Christl said, noting that the device was used to detect counterfeit Viagra in the United States.

As FDASIA becomes entrenched, the law's emphasis on securing the pharmaceutical pipeline, particularly overseas, means that Christl's office will remain busy.

"While ODSIR is not the exclusive office responsible for implementing the provisions specific to foreign facilities," said the ODSIR representative, referring to FDASIA, "ODSIR will work with the other components within the Office of Compliance and Office of Regulatory Affairs as appropriate."

PDA's recent conferences on the pharmaceutical supply chain and cold chain highlighted the complexity of the global distribution network within the industry. The expansion of the Office of Compliance and the development of ODSIR both show that FDA continues to take concerns about supply chain integrity seriously. The *PDA Letter* will continue to follow initiatives within both offices as well as others within the CDER umbrella.

About the Expert

T.J. Christl is currently the Acting Director for the Office of Drug Security, Integrity & Recalls (ODSIR) within CDER's Office of Compliance. Previously, he was the Acting Deputy Director of ODSIR from August 2011 through the beginning of January, 2012. Prior to moving to ODSIR, LCDR Christl was with CDER's Office of Counter-Terrorism and Emergency Coordination where he played a central role in developing CDER's crisis coordination capabilities.

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Microbiologists Key in Preventing Contamination

Rebecca Stauffer, PDA

"If you see something, say something" has been the mantra of public safety campaigns across the country and worldwide for over a decade. While aimed mostly at commuters, this message can also be applied to the microbiologists diligently working to identify microbial contaminants in the pharmaceutical industry.

Not surprisingly, the recent issue of steroid shots contaminated with fungal meningitis shadowed the conference, making the 2012 microbiology conference timelier than usual. From beginning to end, the meningitis contamination issue stayed at the forefront of presenters' and attendees' minds. **Matthew Arduino,** PhD, Lead Microbiologist, Centers for Disease Control and Prevention, opened the conference with his plenary address, "Outbreaks Associated with Pharmaceutical Products," highlighting outbreaks associated with pharmaceutical products his organization has handled over the years.

He began his presentation by describing his role at CDC as being "like a fireman...our lab does a lot of outbreak investigations."

He defined the level of involvement that the CDC takes when it concerns possibly contaminated products. The Agency's main mission involves prevention and preparedness of illness and new health threats as well as risks to national and international healthcare delivery systems.

"So we're more focused on the health providers and patients," he said.

Next, he outlined how CDC is notified of potential threats, pointing out that the Agency gets calls from healthcare facilities, the media, the FDA, and state and local health departments. The latter played a key role in alerting CDC to the outbreak.

"We had an astute state health officer in Tennessee," he said, "who all of a sudden gives a call in late September saying 'we have a cluster of *Aspergillus* meningitis—and this is kind of rare. We think something's going on, and it's all coming from one outpatient clinic,' which then triggered our response."

Taking a cue from public safety campaigns, it's best to recognize and report potential contamination events quickly.

As far as contaminated products, he said there are two main types of contamination: intrinsic and extrinsic.

"Intrinsic contamination," he said, "is product contaminant at the manufacture or at compounding. So it means the product is already contaminated when the user receives it."

On the other hand, "extrinsic contamination is contamination that's introduced during use. It could be via the hands of the healthcare worker, it could be because, 'oh gee, we're using the same syringe more than once,' or how the product is stored."

Regarding outbreaks associated with intrinsic contamination, Arduino admitted that it, "overall for the number of products that are produced, is relatively small." Most lately, however, intrinsic contamination has been associated with compounding pharmacies "who are acting like manufacturers."

The intrinsic contaminations that have happened have occurred due to lapses in infection control. These often bubble below the surface, he indicated.

"Some of these we don't even hear about," he said. "Some of these go even unreported."

At the same time, however, CDC's statistics show that of CDC investigations reported between 1980 and 2012, 23 involved end users, compared to 17 due to manufacturing issues and 11 due to compounding pharmacies. Arduino admitted even that 23 is an underestimate of the issue of end user contamination.

Yet recently the numbers have been changing.

In the 2010s, "more than half of the outbreaks we've investigated have been due to compounders," he said, citing figures comparing outbreaks at the manufacturer level, at compounding, and at the end user level from the 1970s to today.

When it comes to the organisms involved in contaminated products, infections generally differ among those due to compounders, manufacturers, and end users with the latter involving a plethora of viruses. ➤

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"If we look at the compounding pharmacy," he said. "Again, it's a group of gram negative organisms plus fungi. If we look at the manufacturer, we've seen endotoxin. We see a lot of outbreaks due to *Burkholderia cepacia*."

Yet, these outbreaks share one commonality.

"Do you know what that all represents," he said. "Water. Water quality. A lot of these bugs are found in water."

Arduino followed this section of his presentation with some examples of outbreaks involving manufactured products. First, he highlighted an outbreak of sterile peritonitis during the '90s that occurred in Pennsylvania among peritoneal dialysis patients. In looking further, investigators found endotoxin in large bags of saline that were cycled. All of this came from a single manufacturer. Water issues were the likely cause of this outbreak.

Next, he discussed saline units contaminated with *Ralstonia pickettii*. These units were used for pediatric ICU patients receiving endotracheal suctioning. Although the product filter was sterilized, *Ralstonia* was still capable of being passed through due to sterilization limitations. Outside the United States, endotoxin contamination occurred at a site in Brazil within two IV solutions: ringers lactate and metronidazole.

Outbreaks among compounding pharmacies have included heparin saline flush syringes contaminated with *Serratia marcescens* and *Pseudomonas fluorescens*, ophthalmic solutions contaminated with *Pseudomonas aeruginosa* and *Burkholderia cepacia* (leading to blindness from infections), total parenteral solutions contaminated with *Serratia*, and of course, the recent outbreak of meningitis among recipients of epidural steroid injections.

"These outbreaks continue to highlight differences between pharmaceutical manufacturing companies and what compounding pharmacies are doing," he stated.

Arduino then delved into the most recent outbreak—*Aspergillis fumigatus* contaminated Methylprednisolone acetate lots.

"We have again, a pharmaceutical product, which, again, there have been cases of meningitis occurring, and it would have been probably still percolating along below the radar if somebody did not say 'wait a minute, there's something wrong going here.' And that's where we get the call from Tennessee," he said.

He also noted an earlier outbreak in 2002 of meningitis caused by *Exophiala dermatitidis*. Patients developed meningitis after receiving epidural injections of methylprednisolone. These lots also came from a compounding pharmacy.

On the end user side, he recounted numerous instances of unsafe practice, including nurses receiving bounties for the amount of EPO recovered at a hemodialysis center and fentanyl painkiller patches being diverted for illicit use.

So how does CDC work with industry to ensure patient safety?

"We also actually partner with manufacturers and other groups to say 'we need to find a way to fix some of these things.' We help develop evidence based guidelines and clinical alerts...we are now actually developing assessment tools and checklists that allow facilities to proactively look at their practices," he said, outlining the steps his Agency is taking.

"The bad news is we continue to hear about breaks in practice," he said. "We're First World. We know about how we should be doing safe injections. But we still see safe injection practices not being followed."

During the Q&A that followed his presentation, Arduino expanded on his views concerning oversight of compounding pharmacies.

"I think from the compounding pharmacy perspective there is a need for some oversight," Arduino said. "Because what's happening with some of these compounding pharmacies is they're actually becoming manufacturers...if you really look at state law that regulates compounding pharmacies each product is supposed to be made *for a patient with a prescription*."

He then said that those compounding pharmacies that are, in essence, manufacturers, do not appear to be adhering to industry GMPs and there are questions as to whether they are following USP 797.

From the FDA, **Rick Friedman**, Associated Director, Office of Manufacturing and Product Qualty, CDER, provided that Agency's perspective on pharmaceutical microbiology and the meningitis crisis. He opened his presentation by sharing an anecdote from the start of his career. At that time, he was deciding between a career as a toxicologist or microbiologist.

"Either way you're looking at contamination," he said. "Or you know, levels of risk so they're kind of an allied field in some ways."

Friedman went on to describe further the role of the microbiologist specifically ➤

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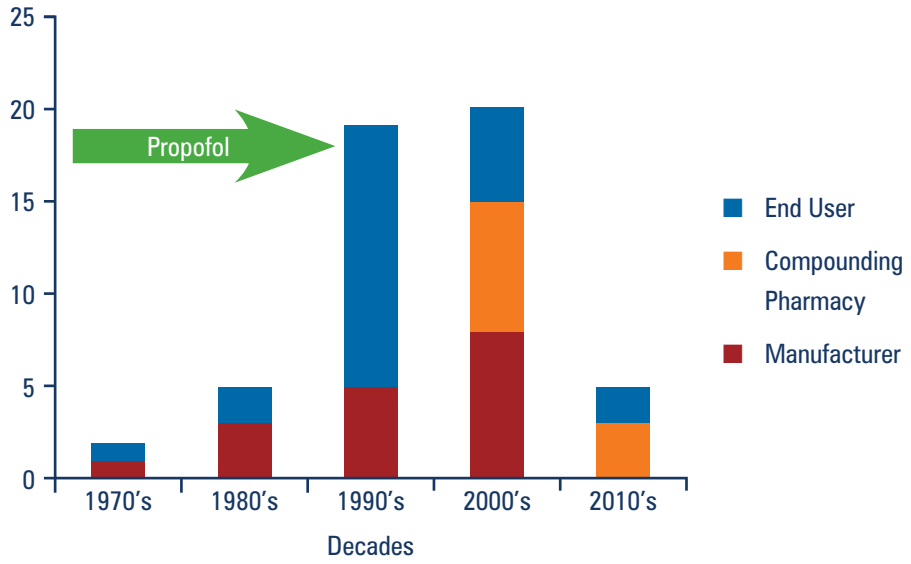

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RESUSCITATION OF MICROORGANISM	Quick-dissolve pellet, no pre-incubation	Quick-dissolve pellet, no pre-incubation	Incubate suspension for 30 minutes before inoculation	Incubate suspension for 30 minutes before inoculation
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within pharmaceutical manufacturing as well as his thoughts on the state of the field.

"I've seen some things recently that do worry me a bit. I think you all know what some of those things are," he said.

We're First World. We know about how we should be doing safe injections. But we still see safe injection practices not being followed

The first point of his presentation is that "the patient is the customer." Elaborating further, he said "we talk about the idea of risk. It's interesting to think of it from a statistical perspective...but in the end there's no substitute for a sufficient amount of data to really characterize the quality of a product. We tend to have very small sample sizes and nowhere is that more true than the pharmaceutical laboratory when we are looking at something like sterility or looking for contamination because contamination is not uniformly distributed."

Ultimately, a pharmaceutical microbiologist cannot totally be sure about the risk factor "unless you can guarantee one thing: that you have process consistency. You have a state of control from beginning to middle to end of the batch. And you maintain that state of control."

He then spoke about risk from a commercial versus a patient perspective. There is *producer's risk* meaning adequate product is rejected and *consumer's risk* when defective product is accepted and sent out the door. ***(1)*** These two risk probabilities depend on "inspecting and scrapping good product" or "the costs of shipping bad product," the latter of which is a huge concern within pharma.

"Our first concern is the welfare of the patient so we tend to err on the side of producer risk rather than have that risk transfer to the consumer," Friedman pointed out.

"I think some of the failures we've seen at big, medium, and small companies have a lot to do with the robustness of their quality system," he added. Sometimes companies fall into the trap of only looking at larger, more apparent issues while putting smaller issues aside. Other times companies ignore larger, systemic issues for tackling easier to correct smaller issues. The key to achieving a robust quality system that can tackle both large and small issues begins with senior management's Commitment to Quality, help up by quality risk management (QRM) and knowledge management (KM). At the same time companies need to move away from a reactive quality control viewpoint to a proactive quality assurance paradigm.

"The drug business is a different business," Friedman emphasized. "And that's why it does have some regulation in areas that other businesses don't."

On the role of the pharmaceutical microbiologist, Friedman asked "are qualified microbiologists at your company doing the following: conducting tests in the laboratory—well sure, right, that's the traditional microbiology role...so that's basic responsibility but it is not the whole role." In fact, Friedman said there should be even greater roles for microbiologists within industry, pointing out he would like to see microbiologists involved with teams responsible for design, control, and validation decisions. During an investigation, his group needs to see "judgements that require microbiological understanding, *deep* microbiological understanding."

"Microbiology SMEs," he said therefore. "are a critical part of the multidisciplinary team. Indispensable, and they need to be there."

Finally, Friedman closed his presentation with an overview of contamination outbreaks among compounding pharmacies. He noted that incidents involving compounders have been ongoing for several years including lots of methylprednisolone acetate containing fungi produced by a South Carolina pharmacy in 2002 that led to the death of one patient.

"Our commissioner, Dr. Kessler, in the late '90s talked about the grave risk, the grave hazard, by compounding products—blindness, and the most worrisome outcome...fatalities due to the past history that he was observing of pharmacies in the late '90s," said Friedman citing earlier concerns about compounders. He then showed a list, comprising three slides, of 20 contaminated sterile compounding product events since 1998 compiled by the Institute for Safe MedicatIon Practices. In fact, not every compounding contamination incident was featured on this list.

"You don't see this in the pharmaceutical industry," he said referring to contamination events at compounding pharmacies. "You see a couple of problems that I've showed you and they are worrisome...but those are blips on the screen that are less frequent."

During the final session of the conference, a forum where attendees could ask questions of a panel of FDA regulators consisting of **Julie Bailey**, PhD, Supervisory Biologist, Center for Veterinary Medicine, **Cynthia Jim**, Consumer Safety Officer, and **Rebeca Rodriguez**, National Expert Investigator, Office of Regulatory Affairs in addition to Friedman, compounding pharmacies remained a topic of interest. The first question from the audience concerned how the New England Compounding Center appeared to be shipping out massive amounts of product, like a regular manufacturer, without falling under FDA regulations, and instead falling under, apparently lax, oversight at the individual state level.

"The system is very complex," Friedman answered. "I think that the detectability of these problems is difficult because it's only once you start seeing a cluster do you realize that contaminated product may be responsible." At the same time, such clusters often initially pop up on the radar of the states tasked with monitoring pharmacies before reaching the attention of the FDA. Considering that every hospital has its own pharmacy, it can be hard to keep track of poor prac-

tices within pharmacies until events occur. Still, since the late '90s, Friedman said, referring back to the Commissioner Kessler's prescient view, there has been awareness that compounding pharmacies were becoming "quasi-manufacturers." The relationship between compounding and manufacturing became even murkier when hospitals and other medical facilities began outsourcing their needs to compounders that were sending out large batches of product.

From a regulatory perspective, he cited the challenges of reconciling state and federal laws as well as court decisions, including the recent Supreme Court striking down portions of a law detailing regulation of compounding pharmacies.

"So what happens," Friedman said, "they're in a limbo, these companies that you're talking about."

Another attendee then commented that going back to Arduino's presentation, something like the meningitis outbreak could hide below the surface. But all it takes is one person to notice something amiss, citing the Tennessee health official who first notified CDC about fungal meningitis infections among patients at a pain clinic.

In a way, pharmaceutical microbiologists carry the same vital role within their laboratories. By carefully analyzing medicines and collaborating across departments, microbiologists play a huge role in keeping the medicines safe from contamination. Anyone who attended the microbiology conference could not help but leave knowing that microbiologists play an important role as the "eyes and ears" of the industry, like the commuter who reports the suspicious package on the train platform

References

1. Colton, Jim. "Statistical Tools for Pharmaceutical Manufacturing," *Quality Digest*, Dec. 2011.

About the Experts

Matthew Arduino, PhD, joined the CDC's Hospital Infections Program (now Division of Healthcare Quality Promotion) in 1988 as a Research Microbiologist in the Hospital Environment Laboratory Branch.

Julie Bailey, PhD, has been with the Food and Drug Administration, Center for Veterinary Medicine since 2002. She is currently the Team Leader of Generic Team I in the Division of Manufacturing Technologies.

Rick Friedman is the Associate Director, Office of Manufacturing and Product Quality, Center for Drug Evaluation and Research (CDER), Office of Compliance, FDA.

Cynthia Jim has been a member of Team Biologics since October 2004. As a member of Team Biologics she has conducted inspectional and investigational work for the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), occasionally work for local district offices.

Rebeca Rodríguez is a National Drug Expert Investigator from the Office of Regulatory Affairs, FDA, Rockville, MD.

To view photos of these and other experts from the meeting, see p. 10 in Faces and Places.

FDA Remembers Kefauver-Harris Amendments

Rebecca Stauffer, PDA

Fifty years ago, a German drug maker introduced a treatment for morning sickness, welcomed by physicians and pregnant women around the world. The drug, thalidomide, was marketed on data derived solely from animal testing, because at this time, clinical testing to prove safety and efficacy was not required by the U.S. FDA or other regulatory bodies around the world. Though patients enjoyed the benefit of sickness-free pregnancies, thousands of babies worldwide were born with horrific birth defects, and many died before their first birthday. This tragedy ushered in a new era of drug testing worldwide that has prevented a crisis of this scale from occurring again.

While the tragedy's impact in the United States was comparatively minimal at only a handful of victims, public outcry and fear provided the U.S. Congress with the impetus to finally create a legal mandate for comprehensive drug safety and efficacy testing for drug products marketed in the United States. In 1962, Congress passed the Kefauver-Harris Amendments to the Food, Drugs and Cosmetics Act.

On October 2, FDA honored the 50th anniversary of these amendments by hosting a public forum to describe the law and its impact on the industry and the Agency. As FDA expands and changes the offices under the CDER umbrella, this event offered a glimpse into the history of pharmaceutical manufacturing regulations and the regulatory changes within industry.

Margaret Hamburg, MD, Commissioner of the FDA, opened the event by acknowledging the history behind the passage of the Kefauver-Harris Amendments. She referred to these amendments "as some of the most seminal federal acts of the last century. It ushered in a project of utmost importance to our Agency and it has helped advance the public health, our economy, and American leadership in pharmaceutical science."

The law enabled FDA to require "adequate and well-controlled" investigations to show a drug's effectiveness, allow the Agency to inspect facilities to ensure good manufacturing processes, and placed limits on marketing claims.

Over the years the Agency has worked to develop high standards for reviewing drugs while also expanding efficient processes to "fast-track" needed medications to the marketplace.

On the amendments' effect on biomedical research, **Stephen Spielberg,** PhD, MD, and Deputy Commissioner for Medical Products and Tobacco, discussed the improvements in controlled studies since the 1960s.

"Somebody sitting and looking at a 'well-controlled' study in 1960 would barely recognize what it means today," he said.

Speaking on behalf of Canadian thalidomide survivors, **Mercedes Benegbi,** Executive Director of the Thalidomide Victims Association of Canada and a thalidomide victim herself, said that Americans should "never forget that your country, the United States of America, was a model or rigor and tenacity throughout the world when the thalidomide tragedy occurred, and that you have the duty to maintain it."

Noting that she was born the same year of the enactment of the Kefauver-Harris Amendments, Benegbi expressed that "it is an honor for me to share my years with the Kefauver-Harris Amendment Act."

Following a standing ovation for Benegbi, **Deborah Autor,** Deputy Commissioner for Global Regulatory Operations and Policy at the Agency, addressed the amendments' impact on enforcement and some of the challenges regulators faced.

President John F. Kennedy hands Sen. Estes Kefauver the pen he used to sign the 1962 Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act. Those looking on include Frances Kelsey, second from left, the FDA medical officer who refused to approve the new drug application for Kevadon, the brand name for thalidomide in the United States.

"The thalidomide tragedy itself created a significant challenge for FDA drug staff. Over 1200 physicians were given thalidomide in the United States for testing without a meaningful tracking system," she said. The Agency personally contacted each of the physicians involved in an effort to confiscate the drug.

"Implementing the efficacy requirement for drugs already on the market was also a massive undertaking for the Agency," added Autor.

The law also resulted in the expansion of GMPs across the industry. She cited numerous pre-Kefauver-Harris drug manufacturing incidents that harmed Americans, including an incident where a vaccine manufacturer produced a polio vaccine that contained live polio virus instead of the inactivated virus. This led to numerous people developing paralysis from the resulting polio fever and some deaths.

"So how does this all look today?" she asked. "We continue our efforts to ensure that drugs are not on the market unless they prove safe and effective."

Somebody sitting and looking at a "well-controlled" study in 1960 would barely recognize what it means today

Joseph Levitt, Chairman of the FDA Alumni Association, provided the perspective of an FDA alumnus, referring to the amendments as an example of "regulation done right."

"And how many times have the FDA heard people say that about us," he asked rhetorically. "So 'regulation done right' ought to be the tagline for this program."

He then went on to discuss how FDA alumni have worked to uphold the amendments and work with the Agency on changes to subsequent regulations.

Finally, **Douglas Throckmorton,** MD, Deputy Director, CDER, offered his opinion of the Kefauver-Harris amendments impact on modern medicine.

"The history of drug development in the United States is one of continued progress punctuated by transformative events," he said. "The Kefauver-Harris Amendments passage is one of those transformative events."

Like Spielberg, he noted the changes in product development and regulation from the 1950s to today.

"As a result, the FDA is the gold standard—our review process, our drug development process is considered the standard by which other parts of the

Continued on page 43

Regulatory Briefs

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

North America

New Law Seeks to Protect Supply Chain

On Oct. 5, 2012, the SAFE DOSES ACT was signed into law as a measure to help protect patients from risks associated with use of resold, stolen and improperly stored medical products including medicine re-entering the legitimate supply chain.

The Act strengthens the criminal code to increase criminal penalties for medical product cargo theft and provides law enforcement teams with new tools in order to deter this criminal behavior.

This law targets sophisticated criminal organizations that are stealing large quantities of medical products by hijacking tractor trailers at rest stops, breaking into warehouses and evading alarm systems and other security countermeasures and then re-introducing medicines into the legitimate supply chains (i.e., pharmacies and hospitals), oftentimes using forged shipping documents and product labels.

Specifically, the SAFE DOSES Act:

- Creates a new federal criminal statute, 18 U.S.C. 670, focused on medical product theft
- Increases sentences for the theft, transportation and storage of medical product cargo
- Enhances penalties for the "fences" who knowingly obtain stolen medical products for resale into the supply chain
- Increases sentences when harm occurs or trust is broken – in other words, where injury or death results from ingestion of a stolen substance or where the defendant is employed by an organization in the supply chain
- Provides law enforcement tools such as wiretaps
- Provides restitution to victims injured by stolen medical products

Improperly managed medical products pose a danger to patients because they can be ineffective, or even harmful to patient safety. For example, in 2009, thieves stole a transport truck containing 129,000 vials of insulin (valued at $11 million) in North Carolina. Several months later, the FDA received a report that these vials had been reintroduced into the supply chain when a diabetic patient reported to a medical center in Houston with an adverse reaction after using insulin from the stolen lot. Vials from this lot were located in pharmacies in 17 states. It has been reported that two additional patients experienced adverse reactions using product from this stolen lot.

Brief submitted by Brian Goldsworthy, Director of Corporate Security, GlaxoSmithKline

U.S. FDA Announces New User Fee System

Effective Nov. 14, FDA personnel and contractors will use the Agency's new user fee system (UFS) to maintain information about individuals, organizations, and companies required to pay user fees. Each UFS file will contain the following: contact person's name, phone number, fax number, and email address, entity remitters' Federal Employer Identification Number (FEIN), individual remitters' Taxpayer Identification Number (TIN), company name or the organization name, and data Universal Numbering System (DUNS) number and business address.

The UFS will also be used to store application information collected when submitters create coversheets in order to pay user fees. This information will include the type of application, waiver and exemption status, and SBD number. Additionally, the UFS will include fee processing and billing information such as billing details, adjustments to invoices including credit and debit memos, and receipt information including date, mode, and amount of payment.

Information collected in the UFS will be used primarily to assess and collect user fees as well as provide Web-based features including information on transactions and payment status.

Key Regulatory Dates

Comments Due

January 18 — U.S. FDA Seeks Comments on Custom Device Exemption

February 11 — U.S. FDA Seeks Comments on Medication Error Guidance

February 28 — EMA Seeks Comments on Annex 17 Updates

EMA Seeks Comments on Annex 15 Draft Guideline

Draft Guidance on Medication Errors Available

The U.S. FDA has published a draft guidance for pharmaceutical manufacturers titled *Safety Concerns for Product Design to Minimize Medication Errors.* The guidance offers sponsors of investigational new drug applications, new drug applications, biologics licensing applications, abbreviated new drug applications, and non-prescription drugs marketed without approved applications a new set of principles. These principles use a systems approach for lessening medication errors due to the design of the product.

Two other guidances will follow the release of this guidance as part of a series of guidances that seek to minimize risks leading to medication errors.

Comments are due by Feb. 11, 2013.

U.S. FDA Seeks Comments on Custom Device Exemption

The U.S. FDA is currently seeking input regarding custom device exemption cri-

teria under FDASIA, specifically focusing on information about appropriate uses for the exemption. FDASIA allows for custom devices to be exempt from performance standard or premarket approval requirements. Comments are due by Jan. 18, 2013.

Europe

EMA Releases Draft Annex 15 Paper

In early December, EMA published a draft concept paper concerning the revision of Annex 15, "Qualification and Validation" of the EU-GMP-Guide. Comments are due by Feb. 28, 2013.

Originally published in Sept. 2001, Annex 15 dealt with the qualification and validation regulatory requirements for European GMP. Since that time, the European GMP environment has undergone numerous changes due to the introduction of ICH Q9 and Q10 as well as updates to the Quality Working Party's guidelines on process validation. Changes to other parts of the GMP guide also impact Annex 15. The draft guideline is expected to be released in Dec. 2013 with comments due on the draft guideline by March 2014. The document is expected then to be finalized by Oct. 2014.

EMA Seeks to Expand Annex 17 to Cover Real Time Release Testing

EMA has published a draft concept paper with updates to Annex 17 of the EU's GMP Guide. Annex 17 concerns parametric release. Due to the adoption of ICH Q8, Q9, Q10, and Q11 guidelines as well as the Quality Working Party's Guideline on Real Time Release Testing, there have been significant changes concerning testing of pharmaceutical products. At the same time, Annex 17 will be updated to areas beyond just sterility testing, which was the guideline's original focus.

Ultimately, the updated Annex 17 will illuminate to which extent Q8, Q9, Q10, and Q11 need to be followed for Real Time Release Testing.

Comments are due by February 28, 2013.

International

ICH Publishes Concept Paper on Q7 Q&A

ICH has published its final concept paper, a Q&A document, on ICH Q7 on GMPs for active pharmaceutical ingredients. Following approval of Q7 in November 2000, questions arose over interpretations of sections concerning the life cycle approach and technical issues regarding the harmonization of inspection expectations.

The Q&A document should address a review of the current Q&A on APIs currently conducted by PIC/S teams, application in supply chain control, outsourcing management, monitoring of impurity profiles, quality systems, and applicability to biologics, and the relationship with Q5D and GMP expectations during manufacturing for clinical trials, and the impact of ICH Q7, Q8, Q9, Q10, and Q11.

Publication of the Step 2 and Step 4 documents is expected sometime in 2014.

Zoom Off to the Future at the 2013 Annual Meeting

2013 Annual Meeting • Orlando, FL • April 15-17, 2013 • pdaannualmeeting.org

Rebecca Stauffer, PDA

The *PDA Letter* spoke with **Hal Baseman,** COO, Valsource, and **Maik Jornitz,** Vice President, G-Con LLC, the co-chairs for the 2013 Annual Meeting Program Committee about the upcoming meeting and what members can expect.

What can you tell us about the upcoming meeting at this point?

Baseman: As with all of our Annual Meetings, this year's conference is a science and technology based event. The 2013 Annual Meeting specifically focuses on advances in modern manufacturing, the challenges currently faced by the industry, and the challenges that we will face in the next few years.

There are three basic tracks of papers, biological science systems, sterile product manufacturing, and quality. Within those tracks we're tackling new subjects and areas of focus, as well as subjects that the industry has been facing for several years.

Jornitz: It's a very unique meeting because it will show a glance into the future of the industry. This meeting has a variety of different options where you can cherry-pick the different areas you want to know about. The industry and our members want to know what's happening in the future and trends which are occurring. It is one of PDA's activities to scout globally for such trends of science and technology as well as regulatory topics and this conference will present these findings.

The entire industry is in a shift to more efficiency; legacy models don't work any longer. When you look at the competitive pressure which is happening then you have to change your technology perspective. And besides that the industry desires to become faster, more flexible and scalable. The conference addresses the desires by showing up-coming process and product technologies.

What are some of the events/speakers you'd like to highlight?

Baseman: Some of the areas that will be presenting on are single use systems, new investigation techniques, drug shortages, counterfeiting, biosimilars, and innovative methods for sterile manufacturing. In addition, sessions and presentations will explore current issues facing our industry:

Understanding that a key issue in the industry over the last few years has been glass defects and delamination, an important presentation will explore considerations for manufacturers seeking to move from glass to plastic containers.

We will also build on some of the more successful efforts from last year's Annual Meeting, including a session on career development, focusing on the tools and approaches one can use to advance one's career.

Outsourcing of sterile product manufacturing and testing continues to be an area of interest to the industry. The distinct advantages and unique challenges presented by outsourcing will be presented and discussed during this year's sessions.

> *A lot of the industry is actually moving and switching to a single use technology*

Jornitz: The session on new production methods like transgenic plants or plant-made pharmaceuticals is a topic of interest for me. I would like to know more about the viability of such technology, regulatory thought process and process efficiencies.

I think Session C is very interesting because it's single use technology that addresses the validation of single use technology. And single use technology is really an up and rising technology within the industry. A lot of the industry is actually moving and switching to a single use technology, so it's always interesting to hear about the validation issues which we have with that technology.

There are presentations on new contaminants within the industry, one by **Anders Vinther,** PhD, (Head of Biologics Quality at Genentech and Roche), and I am very interested in this topic as the Leptospira contamination potential needs to be discussed to evaluate technologies and methods to eliminate such contamination risk.

For new members, as well as members who've never attended the Annual Meeting, can you describe some of the benefits that members get by attending?

Baseman: Attendees will benefit from the knowledge gained directly from the presentation of important papers. In addition, attendees will have the valuable experience of participating in and listening to exchanges during interactive question and answer sessions. The sessions are designed for a significant portion to be devoted to question and answer exchanges. Moderators are encouraged to get the audience into the conversation, not just ask a couple of questions and go on, but to really get into a good exchange of information. This discourse is an educational opportunity, as well as a strong networking opportunity.

There are carefully planned networking and social activities, where professionals in the industry can meet, in a less formal manner, and discuss the topics of the day. This is an important chance for new members to gain more knowledge and get a better feel for the industry.

And one other thing, that is the interest group sessions. PDA interest groups are unique in the industry; they are not just

Continued on page 43

Follow Up on the Latest Process Validation Trends

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Program Planning Committee

Interested in learning more about the latest approaches to process control and validation? Want to interact with leading experts on process validation, including the team behind *PDA Technical Report No. 60, Process Validation: A Lifecycle Approach*? Looking for the latest on U.S. FDA and EMA viewpoints regarding process validation and regulatory submissions? Then, PDA invites you to attend its upcoming *Process Validation Workshop* scheduled in May.

FDA Guidance, *Process Validation: General Principles and Practices,* published in January 2011, will be the main focus of this workshop. This guidance approaches process validation from a lifecycle perspective and incorporates the current thinking of the Agency on the stages of process validation: process design, process qualification and continued process verification. The tools and concepts of statistics, risk management and quality systems will also be addressed. U.S. and European regulatory experts, including some who worked on the guidance, will offer first-hand perspective on the latest issues, problems and future viewpoints. These experts will offer tips on what investigators are looking for when they visit your plant.

Other topics include case studies and plans for the validation of challenging processes, use of statistics in process validation, and lifecycle management.

This meeting is open to all involved with process validation, including those working in manufacturing, formulation, compliance, engineering, QA/QC, development regulatory affairs, research and development, technical operations, and of course, validation. Everyone in these areas from technical contributors to senior scientists and managers are urged to attend.

If you are actively involved in planning, conducting and/or evaluating validation activities, you cannot miss this workshop! By attending this meeting you can take part in understanding and setting future process validation practices.

Experts will offer tips on what investigators are looking for

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

11-13 February 2013

Maritim Hotel
Ulm | Germany

WORKSHOP | CONFERENCE | EXHIBITION

https://europe.pda.org/ParDrug2013

TRI to Offer Five-Day Cold Chain Training Course Series

Bethesda, MD • March 18-22 • www.pda.org/ColdChainWeek

Rafik H. Bishara, PhD, Leader, Pharmaceutical Cold Chain Interest Group (PCCIG), PDA

Leaders of pharmaceutical, biotech, medical device companies, and generic manufacturers, distributors and wholesalers are being challenged with a new regulatory guidance that requires the temperature sensitivity of all shipments to be defined and the distribution methods to be qualified. Shipping and storage methods must be qualified and appropriately controlled and/or monitored to prove the product was not harmed by the ambient environment.

This means that shipments that have historically been distributed in the "ambient" environment are being required to have temperature controls or monitoring applied. The increase in costs associated with this added control or monitoring is a large concern; therefore, companies are making it a priority to create strategies that reduce the financial impact of these new GDP expectations.

In addition, the integrity of the supply chain, including security of pharmaceutical products, is receiving a lot of attention by regulators and the pharmaceutical/biopharmaceutical industry to ensure that the quality and safety of their medicines are not compromised before reaching the patient.

With all of these factors in mind, I invite industry participants concerned about the integrity of the pharmaceutical supply chain to attend a five day training series, *Pharmaceutical Products Supply Chain Integrity*, in March at PDA's Training and Research Institute (TRI). The series will consist of three courses.

The title for the course delivered for the first two days, March 18–19, is "Global Regulations and Standards; Influences on Cold Chain Distribution, Packaging Testing and Transport Systems." This course will provide the participant with an introduction to global regulations, industry best practices and public standards that relate to the handling, storage and distribution of the temperature controlled pharmaceuticals. Thermal package development and qualification will be discussed along with a case study that will address how to deal with temperature excursions from trip monitoring data.

On the third and fourth days of the series, March 20-21, TRI will deliver the course, "From Cold Chain to Temperature Controlled Good Distribution Practices (GDP)." The focus of the third day will be to learn and discuss the tough choices involved in meeting the expectations of Good Distribution Practice. This will be done by reviewing the best practice guidance provided in *PDA Technical Report No. 39, Guidance for Temperature-Controlled Medicinal Products: Maintaining the Quality of Temperature-Sensitive Medicinal Products through the Transportation Environment*, *PDA Technical Report No. 46, Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User, PDA Technical Report 52, Guidance for Good Distribution Practices for the Pharmaceutical Supply Chain,* and *PDA Technical Report No. 53, Guidance for Industry: Stability Testing to Support Distribution of New Drug Products,* and by discussing practical applications for implementing these new guides. *PDA Technical Report No. 58, Risk Management for Temperature-Controlled Distribution* will also be mentioned and participants will be introduced to PDA's Technical Report portal.

> ***Thermal package development and qualification will be discussed***

The course notes will offer the participants a copy of each of the four relevant PDA published reports.

On Day 4, participants will learn and discuss additional choices involved in meeting the expectations of Good Distribution Practice by analyzing Technical Reports 46 and 52 in greater detail. Multiple case studies and scenarios will highlight some of the do's and don'ts of the Good Pharmaceutical Products Supply Chain Integrity.

An overview of the principles of security for good pharmaceutical products supply chain integrity will be presented on Day 5, March 22, of the training in the course titled "Pharmaceutical Products Supply Chain Security." This will include discussions on such topics as Transported Asset Protection Association (TAPA) standards, supply chain security management systems, cargo risk assessments, and security monitoring processes.

Students can opt to attend any of the three courses, such as just one or two courses, or all three. Discounts apply for individuals registering for multiple courses.

About the Author

Rafik Bishara, PhD, has become one of the most respected figures in the pharmaceutical cold chain distribution sector, following a distinguished 35 year career with Eli Lilly & Co. as Director, Quality Knowledge Management and Technical Support. He has been acting as mentor and training adviser to the WHO/PDA "Pharmaceutical Cold Chain Management on Wheels." Dr. Bishara is a member of the Editorial Advisory Board of Pharmaceutical Outsourcing Journal; Life science Leader Magazine; and the Board of Advisors of BioConvergence, LLC, and MARKEN LLP. Dr. Bishara's current focus includes supply chain integrity and security.

FDA Remembers Kefauver-Harris Amendments continued from page 37

world aspire to. First, the Kefauver-Harris Amendments fundamentally changed how we develop and use drugs in the United States beginning with requirements that products demonstrate efficacy before they're on the market for a defined patient population," he said. "Meeting this standard required the development of a whole new science. A science of trials conducted of statistical analysis."

Hamburg then presented the Frances O. Kelsey Award to the FDA Alumni Association in recognition of the efforts the Association to support the Agency's activities. Named after the drug reviewer who denied the application for thalidomide, for the most part sparing the United States from the disastrous effects of the medicine, this award is given annually to an FDA employee who shows courage and scientific decision-making in the course of working for the Agency.

While the business of developing and marketing products that involve dangerous substances can never by 100% safe, the system of clinical safety and efficacy testing ushered in by the 1962 Kefauver-Harris amendments has directly resulted in strengthening protections for patients who consume drug products.

Zoom Off to the Future at the 2013 Annual Meeting continued from page 40

venues for focused presentations. They are designed to facilitate an open forum, an exchange of information, and further discussion of topics raised during the previous meeting sessions.

Jornitz: First of all, as usual it's a great networking event. The attendees meet their peers. You can discuss your successes, questions and possible problems with your peers. Instead of investigating yourself and spending your time and resources, you can ask your industry peers, and therefore you get answers right away. You don't have to invent the wheel over and over again.

From a conference viewpoint, you have a variety of different topics, one can pick and choose from. This Annual Meeting has a large spread of traditional topics and new, progressive sessions. You have a basket of opportunity to learn and also to communicate and to ask questions. That's something which I always find invaluable.

Harold Baseman, Chair-Elect

The Vetting of Technical Report No. 60, *Process Validation : A Lifecycle Approach*

Anyone working on any type of committee can attest that it is not easy to get a large group with strong opinions to agree on anything. It is challenging to use such a group to write a comprehensive, consensus-driven scientific document, which meets the needs of a diverse industry. This is especially true when the document must meet the needs of both small and large molecule processes, address both drug substance and drug product manufacture, meet expectations of both U.S. and global regulatory authorizes, and speak to a technology and methodology not always fully utilized by many in the industry.

The PDA Process Validation Task Force met these challenges and worked with the large and diverse PDA membership to develop a strong technical report that will assist manufacturers in our community.

PDA has long been involved in the preparation of technical reports and education on all aspects of validation and process validation, including the publication of *PDA Technical Report No. 42: Process Validation of Protein Manufacturing*.

PDA was considering a technical report on a more comprehensive process validation approach prior to the publication of the U.S. FDA's draft revision of its process validation guidance in 2008, but that document and PDA's comments* to the Agency about the guidance have influenced the content of the technical report. The comments showed us PDA members need to better understand the principles of validation. Since the guidance was nonprescriptive, regulators needed to understand how the industry planned to meet the expectations and to set the standard by which process validation would be accomplished.

Dialog: The First Step

PDA encouraged its Process Validation Interest Group (PVIG) to take the lead. The PVIG and PDA hosted a series of interactive workshops with FDA and industry in North America and Europe in 2009 and 2012 to: 1) present and explain the content and intent of the guidance; 2) solicit additional responses, concerns, and input from the industry; and 3) assist the Agency in understanding the concerns of the industry in an effort to improve and implement the guidance more effectively.

* A Task Force solicited input from the PDA membership at large and received 400 comments that were considered in the final letter to FDA about the draft guidance. www.alturl.com/tpz55

The second step was to transfer the knowledge gained from the workshop dialog. A Task Force was formed in the fall of 2009 by members of the PVIG who participated in the workshops. The Task Force's purpose was to find ways to transfer the valuable information learned from the workshops back to PDA membership. The group identified the technical report already under consideration by the PDA Paradigm Change in Manufacturing Operations initiative.

Throughout 2010 and 2011, the task force and its leadership met to develop content for the technical report, including insight into best practices and desired practices in anticipation of compliance with the FDA guidance, which remained in draft form. The task force started with approximately 10 individuals, but by 2011, grew to over 35 members representing 24 companies, including representatives from manufacturers of large and small molecule drug substance and drug products, U.S. and global regulators, and validation, statisticians, and knowledge management consultants.

In January of 2011, the FDA released its final version of the Process Validation Guidance. At this point, work on the technical report could proceed without hesitation. Towards the end of 2011 the task force had completed enough of the report to submit it for targeted peer review. Over 1,500 comments from industry experts and validation SMEs were submitted to the task force. A smaller group of 12 task force members met in February 2012 to carefully review and address each comment. Where warranted, the technical report was modified to reflect additional points brought out in the comments. In this way, the technical report benefited from the input of a much expanded membership population. Workshops and meetings continued in 2012, including several PDA regional chapter presentations. These meetings updated membership and obtained further input to be addressed by the technical report.

Step 3: Transfer Knowledge Faster

In the spring of 2012, discussion at the PVIG meeting at the 2012 PDA Annual Meeting indicated that the need for training in understanding and implementing the principles of validation as specified in the FDA Guidance and other global initiatives was becoming a high priority to our members and the industry. The PDA technical report was identified as critical to dispelling misconceptions and avoiding potential misunderstanding related to implementation of the Guidance.

Based on this feedback, the Task Force and PDA decided to accelerate the completion of the technical report. Acceleration had to be accomplished, however, without compromising the quality of the document. To accomplish both the timely publication of the report and to assure the quality of its content, the PDA employed aspects of its new streamlined document planning, preparation, and tracking process. **[Editor's Note:** See "New Process Created for Technical Report Development," *PDA Letter,* Nov/Dec 2012, p. 18.**]**

The new process that PDA has developed for tech reports allowed the Task Force to accelerate their work over the course of the summer in 2012, and led to approval of the technical report by the Board of Directors by September.

A lot of hard work by the volunteers and paid staff was required, however, to achieve this pace. Several face-to-face meetings were held at PDA Bethesda headquarters with a subgroup of the Task Force. Additional input from membership and industry experts was incorporated into the document, redundancies removed, and examples refined. Once completed, the report was submitted back to the full Task Force for final review.

In August 2012, the draft report was balloted by the PDA Science Advisory Board (SAB) and reviewed by other Advisory Boards. The PDA Advisory Boards are comprised of volunteer industry experts and regulators appointed by the PDA Board of Directors and responsible for reviewing and making recommendation to the PDA Board for disposition and publication of PDA technical Reports and other documents.

SAB submitted comments to the Process Validation Task Force regarding the document. Those comments were discussed directly by the report authors and SAB members. Once resolved, the SAB recommended the Board approve the report. The modified draft was then submitted, along with the SAB recommendation to the PDA Board of Directors for final approval. It is important to note that the PDA Board of Directors is also made up of technical subject-matter experts in their own right. The Board did approve the report, and PDA was able to announce the approval and the PVIG was able to premier *Technical Report No. 60, Process Validation: A Lifecycle Approach* at the 2012 PDA FDA Joint Regulatory Conference in Baltimore, allowing for additional input, including feedback from FDA participants.

Final Step: Continued Process Verification

Just as process validation is a continuous process of information gathering and process improvement, so the efforts continue with Technical Report No. 60. FDA officials at the 2012 PDA/FDA Joint Conference by regulators did take the opportunity to review the document. So far, discussions continue with the PVIG and other groups on implementation of the FDA Guidance and Technical Report No. 60. The result of these continued efforts may lead to further modification prior to final publication or development of companion documents.

Technical Report No. 60, like its subject, is a living document, assuring our members of the most up-to-date information on the most important issues they face.

Conclusion

TR-60 will be a guide for those developing, planning and implementing a modern validation program. The report builds on principles presented in ICH Q8-11, the FDA *Guidance for Industry, Process Validation: General Principles and Practices*, and European and global guidance. Based on the process described above, I feel confident that it will be a true reflection of industry ideas, best practices, objectives and desired state. It was prepared by you and vetted by you, the members of PDA. This vetting is what makes this report and all PDA technical reports the most useful, most reliable, and best member driven technical documents in the industry.

Acknowledgements

Special thanks to the dedicated Dr. Scott Bozzone and the Technical Report No. 60 task force, the comment review team, the technical report chapter leaders, the final document preparation team, the PDA Science and Regulatory project management staff, the PDA Programming staff, the PDA TRI staff, the industry SMEs and regulators who reviewed and offered such insightful comments and suggestions on the document, and the membership and attendees at the workshops, meetings and the PVIG — who inspired and provided much of the input for the technical report.

Agents of Change

New products and tragedies are the biggest change agents in the pharmaceutical industry. Not much changes otherwise. In recent years, it seems the latter has been behind change more so than the former. And nowhere else is this more evident than at the largest regulatory authority for drug products—the U.S. FDA. The Agency is always looking for ways to more effectively fulfill its mission of guaranteeing the safety and quality of drug supplies for the public it serves. For over a decade now, FDA has identified drug quality and CGMP compliance as a top priority. It has issued reports and numerous guidances on the topics and also worked more and more closely with foreign regulatory bodies. Despite those efforts, it recently has moved ahead with internal reorganizations to improve its ability to focus on drug quality. The Office of Compliance was reorganized in 2011, and in 2012, CDER announced it was seriously considering creating an Office of Pharmaceutical Quality.

To help PDA members better understand these developments, we chose to take a deeper look at FDA's changes. **Rebecca Stauffer** interviewed officials at the new Office of Drug Security, Integrity and Recalls, which is tasked with, among other things, securing the supply chain. Rebecca worked directly with officials at FDA and used public remarks to provide this informative report. Next, Rebecca talked to **Alan Burns** and **Sue Schniepp,** members of the PDA Regulatory Affairs and Quality Advisory Board, to see what their thoughts were on the proposed Office of Pharmaceutical Quality. The conversation provides some surprising insights.

We are always looking to improve the *PDA Letter,* and for 2013, we made a few decisions. First, we reformatted the Volunteer Spotlight page so it has a more modern look and feel. Instead of the text-heavy look we used in the past, now we provide a nice page-size photograph of our victim, err, volunteer. **Katja Yount,** the Letter's designer, worked with PDA Membership Director **Hassana Howe** in the fall of 2012 to arrange photoshoots of volunteers at the final few meetings of the year. Anil Sawant is the first volunteer featured in the new design, and not only is he a great PDA volunteer, he looks really good in his business suit (see page 8)! Katja and Hassana did a great job revamping this page.

Also, we chose to reduce the page count of the issues in 2013 to 48 pages for most issues by reducing the number of PDA advertisements. There will be no reduction in content, but readers probably will appreciate paging through less ads!

Look to the February issue when we announce the new members of the *PDA Letter* Editorial Committee.

PDA Letter

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PARENTERAL DRUG ASSOCIATION TRAINING AND RESEARCH INSTITUTE (PDA TRI)

Aseptic Processing Training Program

2013 Schedule:

Session 1:
Week 1: February 11-15
Week 2: March 4-8

Session 2:
Week 1: April 8-12
Week 2: May 6-10

Session 3:
Week 1: June 3-7
Week 2: June 24-28

Session 4:
Week 1: August 26-30
Week 2: September 23-27

Session 5:
Week 1: October 14-18
Week 2: November 4-8

The most comprehensive program in the preparation of sterile parenteral products

This two week comprehensive training program, taught by 20 industry leading experts in their fields, with over 300 years of combined experience, will give you and your personnel the training and information needed to properly evaluate and improve your aseptic processes to ensure sterile products. This program provides the perfect balance of hands-on laboratory and lecture training, equipping you with tools and actual experience you can bring home and apply immediately on the job.

For more information contact:
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PDA Training and Research Institute
4350 East West Highway, Suite 150, Bethesda, MD 20814
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Benefits of Attending

- Learn to relate and incorporate each component of aseptic processing into one operation for an overall improved process and finished product
- Understand the theory and practice behind personnel gowning and aseptic technique qualification to minimize risk of product contamination by personnel
- Use proper environmental monitoring techniques combined with a good cleaning and disinfection program to avoid common sources of contamination in your facility
- Learn to incorporate proper documentation practices into your aseptic processing program to facilitate regulatory compliance

Learning Objectives

Upon completion of this course, you will be able to:

- Demonstrate an increased proficiency of techniques and skills relating to aseptic processing
- Evaluate and improve current aseptic processing procedures at your facility
- Limit risk for manual product contamination with airflow visualization studies
- Evaluate your environmental monitoring program to collect appropriate data, identify and interpret trends
- Incorporate proper gowning principles into a complete personnel qualification program
- Describe the importance of filter integrity testing when filtering water, gases, or proteinaceous solutions

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