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PDA Letter

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In This Issue…

PDA℠
Parenteral Drug Association

Connecting People, Science and Regulation℠

The Importance of Secondary Packaging to Parenteral Product Security

Carol Mooney, West Pharmaceutical Services, Inc.

Drug counterfeiting is becoming a major threat to the drug supply chain, endangering both consumers and manufacturers. Once a problem limited to under-developed nations, drug counterfeits are now found in the United States, Europe and Japan. Counterfeiting is defined as the intentional dilution, mislabeling or adulteration of prescription drugs. The proliferation of counterfeit drugs can be seen in the number of cases tracked by FDA, which has grown from 4 in 1998 to 58 in 2004 (www.fda.gov/oc/initiatives/counterfeit). FDA's counterfeit investigations include all dosage forms. To combat this growing problem, a number of global pharmaceutical companies have incorporated layered anti-counterfeiting protection into their secondary packaging. Packaging solutions include color coding, covert printing and buttons with the drug product logo molded into or printed on the plastic.

Identifying effective and innovative delivery systems and components for injectable drugs is a challenge for pharmaceutical packaging engineers. Selecting appropriate secondary packaging is as critical to product success as the selection of an appropriate vial and stopper.

Secondary packaging is a drug's first line of protection, followed by primary closures (i.e., vials and elastomeric stoppers) that directly contact the packaged drug product. Although secondary packaging does not contact the drug, it provides protection in helping to maintain a sterile seal, further contributing to patient safety. In addition, it can incorporate overt, covert and forensic technologies[1] to protect against counterfeiting. Secondary packaging also can include vital information to help identify the drug's authenticity, instructions for proper storage, cautionary statements, and information to guard against dosing errors.

Historically, standard secondary packaging components have met industry needs for injectable drugs. Today, however, these standard components could increase the vulnerability of the drug to counterfeiting. The challenge for pharmaceutical companies is to find ways to identify their products as genuine throughout the supply chain. New technologies developed for secondary packaging systems afford opportunities for pharmaceutical manufacturers to improve the safety of their injectable drugs.

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The aim of this conference is to increase understanding and awareness of European GMP expectations. Participants will include representatives from EMEA, member state health authorities and industry, who will share their expertise on recent developments in European GMPs and be available to meet and discuss topics with conference attendees.

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Message from the Chair

Vincent Anicetti, Genentech, Inc.

Looking to the Future

As incoming Board Chair, I'd like to thank the PDA membership on behalf of all incoming officers for their confidence and support. I am honored to have the opportunity to serve PDA over the next two years and to work alongside a distinguished group of board members. Together with the PDA staff, I believe we have the leadership to realize further success and growth in PDA's 60th year.

Also, I'd like to thank past-Chair **Nikki Mehringer** (Eli Lilly and Company) for her extraordinary leadership of PDA during the last two years. Nikki's dedication and wisdom have served PDA well. I am proud of the accomplishments of the Board and PDA staff during this time. Our organization is in its best financial shape in many years. Our staff at PDA is talented and enthusiastic; **Bob Myers** has built an executive team that is second to none.

Most importantly, PDA continues in its mission to seek scientifically sound solutions to the technical and regulatory challenges of pharmaceutical production and administration. For example, a number new Technical Reports have been introduced over the past year. In addition, PDA's relatively new Biotechnology Advisory Board (BioAB) has been identifying biotechnology issues of interest to PDA members globally and has contributed to the formation of dedicated biotechnology tracks at our conferences. We are committed to providing enhanced services to the growing number of members involved with biopharmaceuticals. Our successful programs in Washington, D.C., and in Langen, Germany, in late 2005 give us a good springboard into 2006.

PDA remains committed to focused scientific meetings that fulfill the needs of our members. The 2004 and 2005 PDA/FDA Joint Regulatory Conferences each broke attendance records. Many other recent meetings, both in the United States and Europe, have been at capacity, as well. We will continue to provide our members with the best *Career-long Learning*℠ opportunities in the industry. One new focus will be to make the Annual Meeting our major manufacturing and QC/scientific forum. This year's Annual Meeting will be the first planned under this criteria, and it will also be the venue for celebrating the 60 years of PDA service to the industry.

To accomodate our growing European membership, we are committed to developing a meeting and training program in Europe that is comparable to that in the United States. Our professional staffs in Europe, led by new Senior VP Georg Roessling, PhD, and in the United States are working on an expanded program, approved by the Board of Directors for 2006, which will be of great value and interest; we are confident Georg will make sure the program is successful. The PDA/EMEA Joint Conference is the prime example of the unique services we are planning for Europe. In addition, we are exploring new additions to our TRI offerings in Europe, which already include "Practical Aspects of Aseptic Processing."

Our Asia-Pacific conference, scheduled November 13-15 in Tokyo, is a great example of the effort PDA members place on international harmonization. No issue over the last 15 years has been more important than regulatory harmonization, and PDA members have been at the forefront. PDA's new leaders are committed to this tradition and look forward to the harmonization challenges we will face during the next two years.

Finally, it is important that PDA develops its leaders for tomorrow. As a former Chapter president, I believe we can use our Chapter system much more effectively in providing leadership opportunities to our newer members. Over the next two years, we will be committed to implementing mentoring and other programs to fully engaged the leaders of tomorrow. I look forward to telling you more about this shortly.

I am proud and excited to serve as PDA's Chair at this time. The footsteps I am left to follow are large, but I am committed to fill them with all the energy and dedication I can give. I look forward to meeting with my fellow PDA members at the Annual Meeting in Anaheim, Calif., this April!

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Recent Sci-Tech Discussions:
Temperature Mapping Tolerances

The following unedited remarks are taken from PDA's Pharmaceutical Sci-Tech Discussion Group, an online forum for exchanging practical, and sometimes theoretical, ideas within the context of some of the most challenging issues confronting the pharmaceutical industry. The responses in the Sci-Tech Discussions do not represent the official views of PDA, PDA's Board of Directors or PDA members. Join at www.pharmweb.net/pwmirror/pwq/pharmwebq2.html.

When temperature mapping what are recognized tolerance (acceptance criteria) for freezers, refrigerators, microbial incubators and stability chambers (e.g. all probes need to be at ±X°C of the mean of all the probes)?

If you quote any values, then please could you also provide citations of where exactly your quoted numbers are coming from.

Many thanks and best regards.

Respondent 1: Temperature mapping tolerances should be based upon the temperature requirements of what is expected to be placed in the controlled temperature chamber. The general notices section of USP XXII-NF XVII provides useful storage definitions/recommended tolerances for many of the components on your list. I hope this helps.

Respondent 2: For freezers, refrigerators, and incubators we simply require that all probes be inside the specified range of the unit; e.g. for a 2-8ºC refrigerator or cold room, all probes must remain inside this range for the duration of the study. OQs are done as empty chambers for 24 hours, minimum. PQs are loaded chambers for 60 hours minimum.

Respondent 3: I tried tackling this same question many months ago and come up completely empty-handed in searching for guidance documents and/or citations. The rule of thumb I was taught by someone much more experienced than I was that regarding this topic, it's whatever you can defend on a sound scientific basis. I agree with the comments…as I have seen the same used at various firms. I've also seen the use of temperature probes immersed in product-placebo to demonstrate that the product remained within the required temperature range. This provided added reassurance in that even if there were aberrant, isolated spikes in the temperature of the actual chamber at various probes (i.e. no more the same probe being out of tolerance for two consecutive readings), the probes immersed in product-placebo demonstrated that the product remained within temperature.

Respondent 4: The temperature tolerances are usually dictated by each company, deriving from their product "limits".

The real problem is if an OOS reading will disqualify your study.

This is a question of how the acceptance criteria of the protocol were written.

Generally, as was mentioned, 24-hour or 48-hour continous monitoring is enough to demonstrate that your process is/is not under control.

There are a few technical problems that you should take in consideration before establishing the temperature mapping approach and the required acceptance criteria....

From all the equipment that you mentioned, I would expect that a relatively new incubator will not exceed a limit of +/- 2ºC.

For freezers, refrigerators, and cold rooms, it would be very rare to not have an OOS. A few causes are:

- The freezer has a defrost cycle.
- Every defrost cycle the Kaye or loggers will monitor this cycle, usually generating an OOS.

The monitoring period started before the freezer stabilized.

The controller sensor and the recorder sensor are inside a glycol tube, consequently less sensitive than your sensors. A decision has to be taken as to whether your sensors should be immersed in the glycol as well.

If you are going to perform two engineering studies, one empty and one with the probes inside the product, and in the empty space we will collect all the information, it is necessary to write a correct protocol. The defrost cycle for the freezers cannot be avoided, so this needs to be addressed in the protocol.

Another thing it is the way to analyze the information. I've seen extended statistical studies performed on incubator temperature studies. The protocol had almost 50 pages of statistical calculations to demonstrate that the temperature distribution was within the limits. In my personal opinion—overkill. Hope that helps.

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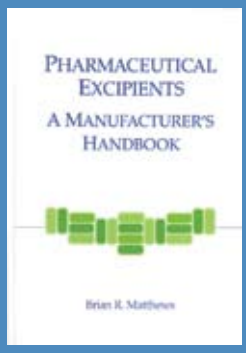

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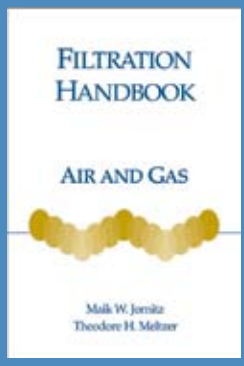

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The Importance of Secondary Packaging to Parenteral Product Security, continued from cover

Secondary Packaging Attributes

Most secondary packaging for injectable drug vials consists of an aluminum shell and a plastic button attached to the shell. In the manufacturing process, a capping machine rolls or crimps the skirt of the aluminum shell under the flange of the vial. The shell holds the stopper firmly in place and creates a tight seal between the vial and elastomeric stopper. This configuration protects the integrity of parenteral products by blocking contaminants from entering the vial, preventing access to the stopper injection site before the drug is administered, and ensuring that contaminants do not settle on the injection site during shipping and storage. Further, the plastic button provides evidence of tampering; when the button is removed, a portion of the aluminum shell tears away and stays attached to the plastic. Buttons that have been removed cannot be reattached properly to the portion of the aluminum shell remaining on the vial. The open top in the aluminum shell is revealed when the button is removed.

Securing the Drug Supply Chain

Manufacturers are increasingly incorporating advanced technologies into secondary packaging to help protect against drug counterfeiting. These technologies offer manufacturers track-and-trace capabilities and covert authentication capabilities from manufacturing to end use.

In a February 2004 report issued by FDA's Counterfeit Drug Task Force (www.fda.org/oc/initiatives/counterfeit), radio frequency identification (RFID) technology was cited for its potential to provide a methodology to track and trace the movement of every drug package throughout the supply chain. According to the FDA report, reliable RFID technology will make copying medications either extremely difficult or unprofitable. The FDA report strongly suggests that pharmaceutical manufacturers incorporate RFID technologies, as appropriate, by 2007. Many pharmaceutical companies are evaluating the acceptability and practicality of secondary seals with RFID tags molded into the plastic button.

Manufacturers are increasingly incorporating advanced technologies into secondary packaging

Because product authentication data embedded into an RFID tag cannot be altered, the electronic profile provides a higher degree of security than paper documents that accompany the drug products throughout the supply chain. Besides allowing authentication in the field, RFID tags also have the potential to provide pharmaceutical manufacturers with the ability to improve inventory management and assign an item-level serial number to each drug vial that passes through a filling line.

Visual Identification

Other item-level technologies that can be incorporated into the secondary seal to thwart drug counterfeiting include printing with spectroscopic inks and applying high-quality, full-color graphics. Information in the form of bar codes, for example, can be printed on buttons in spectroscopic inks that can be read with a scanner only under special lighting conditions.

High-quality graphics can help identify and authenticate drugs as genuine. Because of the sophistication of the printing and molding process, this technology may be difficult for drug counterfeiters to duplicate.

The buttons on vials can be imprinted and molded with conspicuous cautions, warnings and instructions useful during manufacturing, storage and at the point of use. The importance of this feature during manufacturing cannot be understated. When manufacturers ship the filled vials to another plant for labeling, the information printed on the plastic button or seal helps ensure that the product is processed in the correct labeling and final packaging lines.

For some drug products, cautionary statements printed on the button and seal are required. For example, the warning statement "Must Be Diluted" is required on buttons and aluminum shells used to secure vials of potassium chloride for injection concentrate. Cautionary statements, such as "Paralyzing Agent," are frequently used for neuromuscular blocking agents, a class of drugs used during surgical procedures. Other messages may include instructions like "Must Be Refrigerated" or "Store Frozen."

Unique Package Identification

Recording the unique characteristics of a vial's contents on the plastic button and aluminum shell can help reduce medication errors and prevent drug mix-ups in the clinical setting. Information can be printed on the button and shell, or molded into the button and embossed into the shell.

The button and shell provide two layers of identification. The overt messages on the plastic button are the first check on a product's ➤

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Using Nano-Scale Authentication Technologies to Protect Drugs

Jim Rittenburg, PhD, Authentix

Pharmaceuticals are an increasingly lucrative target for counterfeiters. Advanced computer technology—scanners, printers, and copiers—are making it easier than ever for criminals to create bogus packaging that looks identical to the real thing. Some of the most costly drugs are sold in small quantities; therefore, it doesn't take much product to generate sizeable profits for pharmaceutical counterfeiters. Finally, penalties for pharmaceutical counterfeiting are light when compared to the penalties for illegal drug offenses and other felonies.

Each year a growing number of counterfeit drugs find their way into pharmaceutical distribution channels, highlighting the vulnerability of the supply chain. According to the U.S. FDA's 2004 report on counterfeit drugs, counterfeit incidences have been rising precipitously (www.fda.gov/oc/initiatives/counterfeit). In response to this threat, pharmaceutical manufacturers and government agencies are seeking ways to improve the handling, distribution and identification of pharmaceutical products. A range of proven authentication technologies exists for pharmaceuticals and is available for use as critical components in strategies to protect products against counterfeiting. The use of overt and covert authentication technologies is on the rise, with many companies now either already using or preparing to implement these technologies. Although there is no single solution, the thoughtful selection and layering of technologies will provide a highly secure, long-lived and multifunctional countermeasure capability. Key factors in the selection of an effective authentication technology package include:

- Ease of integration onto product and into distribution channel
- Minimal impact on the product manufacturing process
- Presence and compatibility of multiple independent technologies
- Combination of overt, covert and forensic features
- Migration path to new authentication features

Pharmaceutical manufacturers have now begun to proactively build authentication technologies into both product packaging and the dosage form using a variety of sophisticated security technologies.

Another way pharmaceutical manufacturers are safeguarding their products is by thinking ➤

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identity. Because the button covers the top of the aluminum shell, messages printed on this surface provide a covert layer for adding additional information. Examples of the type of information that can be applied to the button and shell include:

- The strength of the packaged drug
- Storage and dosing instructions
- The manufacturer's name and logo
- The drug product's name and logo
- Manufacturing lot and date information

In addition to printed, molded and embossed information, drug manufacturers frequently select unique color combinations for the button and shell to help identify their products. The use of unique color schemes can help differentiate drugs during the manufacturing process, which can help prevent improper labeling.

Some manufacturers also print bar codes and use lasers to etch coding onto the button and shell during the filling process. This coding can also be used to track vials through the manufacturing process.

One cannot overstate the important role secondary packaging serves as the first line of protection for serum, lyophilized and dry powder drugs packaged in vials. In performing this function, the seal serves the most important of purposes: to aid in the safe and efficacious delivery of parenteral drug products.

Note

1. Forensic technologies require laboratory testing.

About the Author

Carol Mooney has extensive experience in the area of closures for injectable pharmaceutical product packages. Currently, Ms. Mooney is working with leading industry groups to identify and develop innovative technologies that address patient safety relative to the growing phenomenon of drug counterfeiting. Carol will discuss these technologies at PDA's upcoming **Pharmaceutical Anti-Counterfeiting Forum,** March 2-3, in Bethesda, Md. Go to www.pda.org/counterfeit2006 to learn more and to register.

small—very small. Nano-scale-based materials are now being applied to anti-counterfeiting applications with a variety of branded pharmaceutical products. These nano-scale materials range from molecular markers that are several nanometers in size to various types of organic and inorganic quantum photonic markers that range from 50 nm to 5000 nm in size.

These nano-scale security markers can be inserted into the drug's packaging, as well as into the drug itself—down to individual dosage form. When used in packaging, nano-markers can be mixed into inks and coatings and applied onto labels, cartons, closure seals, bottle induction seals, vial crimps tops, etc. The presence of nano-materials having unique chemical or spectral characteristics, along with handheld field authentication equipment, allows for easy and accurate field monitoring of pharmaceutical packaging at various points throughout the supply chain. Manufacturers are using these technologies both as an insurance policy in the event they experience a counterfeit attack and to enable proactive field surveillance of their products.

There are several key reasons for pharmaceutical manufacturers to develop simple, yet definitive methods to develop dose-level security:

- Pharmaceuticals are often repackaged after leaving the manufacturers
- Original packaging can be discarded after drugs reach their intended destination
- Counterfeits can contain the right active pharmaceutical ingredient (API) and/or stolen API can end up in fake product

An effective nano-scale-based approach to authenticating drugs is to insert molecular markers made up of trace levels of FDA-accepted ingredients at the parts-per-million or parts-per-billion levels[1]. These markers, which are low molecular-weight organic compounds several nanometers in size, can be detected through simple field-testing kits that take a few minutes to perform.

These nano-scale security markers can be inserted into the drug's packaging, as well as into the drug itself

While field testing of on-package and in-product markers can yield immediate results, forensic inspection (laboratory testing) of the product itself will provide additional confirmatory information and can also provide additional quantitative information that can indicate details, such as the manufacturing site or the intended sales region for the product.

The use of nano-scale materials for anti-counterfeiting applications brings a number of advantages. Since the materials are so small, they are difficult to detect and, thus, nearly impossible to reverse-engineer. Also, very specific detection methods and equipment are required to confirm their presence. Finally, the use of very small materials at very low concentration minimizes the chance of any effect on the appearance or function of the package or product into which they are inserted. In addition, the insertion of these materials can be easily accomplished with little impact on the manufacturing process by, for example, including them as a component of an existing ink on a package or as part of the film-coating solution applied to a tablet.

To realize the full benefit of any authentication technologies, they need to be a part of a comprehensive program that includes assessment of risks throughout the supply chain and supply chain monitoring.

Note

1. Authentix markers have been used in pharmaceuticals in the United States since 1998. These compounds include excipients and substances classified as GRAS (generally recognized as safe). The technology has been through the regulatory process successfully with FDA as part of an NDA application. FDA's 2003 draft guidance, *Drug Product, Chemistry, Manufacturing, and Controls Information,* specifically addresses the incorporation of proprietary markers into new drug products: (Starting at line 283) *Trace amounts of harmless substances added solely as tracers or markers for individual product should be included in the composition statement and the batch formula....Tracers and markers need not be disclosed in the drug product labeling except for those used in parenteral drug products ...."*

About the Author

Jim Rittenburg, PhD, is Vice President, Pharmaceuticals for Dallas-based Authentix. His company provides authentication solutions for pharmaceuticals, consumer goods, industrial goods, petroleum and spirits. Jim will discuss these technologies at PDA's upcoming **Pharmaceutical Anti-Counterfeiting Forum,** March 2-3, in Bethesda, Md. Go to www.pda.org/counterfeit2006 to learn more and to register.

15

Multiple On-Product Anti-Counterfeiting Measures: Audio Conference Excerpt

The following excerpt is from the Aug. 11, 2005 PDA audio conference, "Multiple On-Product Anti-Counterfeiting Measures," presented by David Schoneker, Director, Global Regulatory Affairs, Colorcon. In this portion of the transcript, Schoneker addresses the regulatory concerns associated with the placement of anti-counterfeiting technologies on an oral solid product. He also discusses potential filing criteria. The complete transcript and slide presentation are available at the PDA Publications E-store (www.pda.org/estore).

What about ease of counterfeiting? One of the big problems that people talk about, with a lot of the packaging techniques and with all the improved computer technology that's out there today...no matter what you do, the counterfeiters can use the technology and pretty much fake what you're doing pretty darn well. Well, [with on-product technologies], improved computer technology doesn't really help them at all....It's not computer driven. It's not label driven. It's not printing driven. We're talking about manufacturing techniques and experience and specific procedures that are needed which typically, again, are going to steer your counterfeiters away from your products and have the counterfeiters looking for other targets....At the end of the day, that's your job in the pharmaceutical industry. We can't stop the counterfeiters from counterfeiting somebody's product. You just want to make sure that it's not yours that they're looking at.

What [have we] been doing to see how this works in the regulatory community and move this forward as rapidly as possible? Well, we've been doing a lot. At FDA, in their task force report.... It does talk about the fact that there is existing authentication technologies which have been sufficiently perfected that they can now serve as a critical component of any strategy to protect products against counterfeiting. And they say that you should use one or more on products likely to be counterfeited. And as I told you right now, design features is one of the factors that's going to make that determination about what's targeted. Well, the FDA, when they put this counterfeit task force report together, was very aware of our technology. I had presented it to **Fred Fricke**, the Director of the Forensic Chemistry Lab at FDA. And that initiated discussion at the task force level all the way to the commissioner where they had seen all this type of stuff. And FDA was extremely interested and still is very interested to see how companies can utilize these technologies to think about on-product protection.

Now, taking it one step further, in the counterfeit task force report, it does say that FDA plans to publish a draft guideline on notification procedures for making changes to existing products, such things like addition of taggants or their packaging or their labeling for the purpose of deterring and detecting counterfeit drugs because they want to facilitate and help the industry put these protection systems in place. I will say this though, FDA has backed away from that statement after that report came out. And they've recently stated, and I've had many discussions with them, that... instead of providing sort of general guidance, they've realized that there's so many technologies, so many specific issues, there's no way they could ever put something like that together. What they were going to do instead is they will provide specific guidance based on requests that are made either by pharmaceutical industry people or the authentication suppliers to look for specific guidance on how you can incorporate any particular technology.

But FDA does want to, and they intend to lower regulatory hurdles to make these types of changes happen where scientifically they feel there's enough justification to do it and that there's no impact to the patient's safety....

What does all that mean related to these technologies? Well, the incorporation of any or all of these 5D-ID technologies onto a tablet dosage form, we've determined, provides a very low risk of impact to the dissolution of immediate release drug. We developed quite a bit of model data...to support this hypothesis. However, you would need to demonstrate that on each drug that you wanted to incorporate this on. The key thing here is we're not talking about technologies that are new, innovative things that test the regulatory boundaries....What we're really talking about is utilizing existing excipients and colorants, or ones that already meet FDA requirements. No new excipients or colorants are necessarily used that don't meet the existing requirements that FDA has. So there are no hurdles from that perspective.

So we've been discussing these issues quite a bit with FDA to obtain specific guidance on the incorporation of these technologies into existing drug ➤

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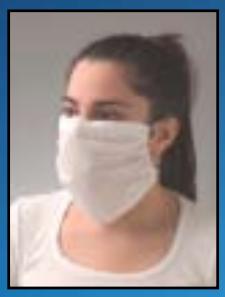

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PDA Calendar of Events for North America

Please visit www.pda.org for the most up-to-date event information, lodging and registration.

Conferences

March 2-3, 2006
2006 PDA Pharmaceutical Anti-Counterfeiting Forum
Bethesda, Maryland

March 27-28, 2006
Cold Chain Management
Bethesda, Maryland

April 24-28, 2006
2006 PDA Annual Meeting
(Conference, Courses and Exhibition)
Anaheim, California

April 26-27, 2006
Process Validation
Anaheim, California

May 8-12, 2006
2006 PDA Biennal Training Conference
(Conference, Courses and Exhibition)
Philadelphia, Pennsylvania

September 11-15, 2006
PDA/FDA Joint Regulatory Conference
(Conference, Courses and Exhibition)
Washington, D.C.

Training

Lab and Lecture events are held at PDA TRI Baltimore, MD unless otherwise indicated.

Laboratory Courses

March 8-10, 2006
Cleaning Validation

March 15-16, 2006
Validating a Steam Sterilizer

March 28-29, 2006
Cross Flow Filtration Evaluations, Scaling and Practical Protein Purification and Separations

March 30, 2006
Process Development and Large Scale Implementation of Membrane Chromatography Devices

April 4-7, 2006
Pharmaceutical and Biopharmaceutical Microbiology 101

April 10-11, 2006
Developing and Validating Cleaning and Disinfection Programs for Controlled Environments

May 8-12, 2006
Aseptic Processing Training Program (session 2, week 1)

May 22-24, 2006
Developing a Moist Heat Sterilization Program within FDA Requirements

June 1-2, 2006
Environmental Mycology Identification Workshop

June 12-16, 2006
Aseptic Processing Training Program (session 2, week 2)

Lecture Courses

May 15-17, 2006
Biotechnology: Overview of Principles, Tools, Processes and Products

September 20-21, 2006
Computer Products Supplier Auditing Model:Auditor Training

Course Series

February 6-8, 2006
Lake Tahoe Course Series
Incline Village, Nevada

March 13-15, 2006
Research Triangle Park Course Series
Durham, North Carolina

April 27-28, 2006
PDA Annual Meeting Course Series
Anaheim, California

May 11-12, 2006
PDA Biennial Training Conference Course Series
Philadelphia, Pennsylvania

Chapters

February 8, 2006
PDA New England Chapter
Rapid Microbial Methods
Dinner Meeting and Plant Tour
Burlington, Massachusetts

February 23, 2006
PDA Southeast Chapter
USP Course — Effectively Using the USP-NF
Raleigh, North Carolina

April 5, 2006
PDA Metro Chapter
First Annual PDA Metro Chapter Day: Microbiology Update
Clark, New Jersey

June 12, 2006
PDA Canada Chapter
Annual Meeting
Vancouver, British Columbia

Europe/Asia Pacific/Middle East

Please visit www.pda.org for the most up-to-date event information, lodging and registration.

EUROPE

March 21-23, 2006
Practical Aspects of Aseptic Processing
Basel, Switzerland

May 25-26, 2006
Translating CGMP into Practical Solutions
Barcelona, Spain

September 27-28, 2006
Visual Inspections
Berlin, German

October 10-13, 2006
PDA/EMEA Joint Conference
(Conference, Courses and Exhibition)
London, England

ASIA/PACIFIC

February 8-10, 2006
USP 5th Annual Scientific Meeting
A Joint Symposium Sponsored by USP, PDA, and Indian Stakeholders
India

November 13-15, 2006
2006 PDA Asia-Pacific Congress
(Congress and Courses)
Tokyo, Japan

MIDDLE EAST

May 17-18, 2006
PDA and the PDA Israel Chapter
Quality Tools for the 21st Century
Eilat, Red Sea, Israel

Multiple On-Product Anti-Counterfeiting Measures: Audio Conference Excerpt, continued from page 16

products. And back in March, I had a major meeting with [CDER and] people from the commissioner's office, all the division directors in new drug chemistry and generics to talk about how these technologies could be incorporated on existing drug products. We believe that the science is there, we've provided a lot of it. [The science] can support the incorporation of these technologies as a minor change. And what we were showing is many of these things can be incorporated, we think, or should be able to be incorporated as an annual reportable type of change. Now, I'm not sure FDA is going to go there. I don't know what the outcome of the guidance is going to be at. We're still waiting for that. But what I would say is, the science certainly seems to justify it. And now we got to see whether FDA is going to go that far with it. But we think there's some real potential for that to happen....

I'm just going to show you a real quick synopsis of some of the data that was presented to FDA that reflects why I'm saying what I just said. If we take a look at pearlescent coatings: We feel there is no impact on dissolution when you in fact put an overcoat of a pearlescent coating on an existing tablet. So if you took your existing tablet as it was today, and you overcoated it with a product called *Opadry fx*—which contains these pearlescent pigments—if you look at this dissolution curve ***[see figures 1 and 2]***, (and this is for an Ibuprofen tablet) if you just have a subcoat on there and let's say that's your existing tablet.... Whatever color it's going to be; it might be yellow or whatever. That's the blue line that says subcoat only. And that coating is a 3% weight gain. If you add over top of that a 1% weight gain of this pearlescent coating, you get a very interesting effect in terms of pearlescence, but take a look. The pink line matches exactly to the blue line. There's no impact on dissolution. If we add a thicker weight gain, we go up to 3% of that weight gain, you get a completely different effect, even though it's the same exact product that you're coating it with. And yet, you'll see there's no impact on dissolution....

So, if we go to the next feature, and that's high definition printing, logos and bar codes. Well, SUPAC and the changes to ANDA and NDA guidance already allows for the addition or modification of a code imprint providing the ink components have been used on a previously proved drug. Well, all the ink components that we use in high definition printing are things that are typically used on all printing. So that's not a problem. And we've coordinated a letter from FDA which clarifies guidance in this area already. So there's no problem if you wanted to add a bar code to an existing product today. You could do that. It is an annual reportable item....

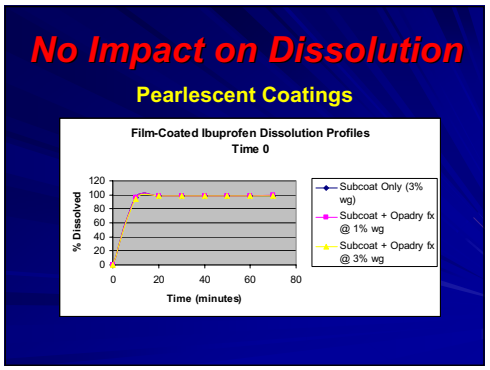

Figure 1

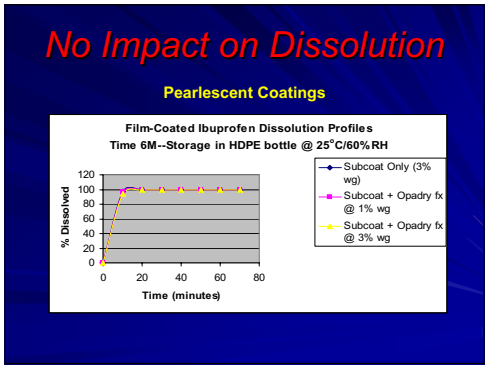

Figure 2

About the Presenter

As the Director of Global Regulatory Affairs, David is responsible for global coordination of Colorcon's worldwide regulatory activities and raw material assets. Most recently, he has been actively involved in developing various anti-counterfeiting authentication technologies, which utilize unique excipient and colorant solutions as well as high definition printing for overt and covert on-product authentication. He serves on the planning committee for PDA's upcoming **Pharmaceutical Anti-Counterfeiting Forum,** and will present at the forum, as well as moderate sessions. Go to www.pda.org/counterfeit2006 to learn more and to register.

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Regulatory Briefs

United States

FDA Publishes Final Dispute Resolution Guide

FDA published its final guidance, *Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP*. The guidance was developed as part of the FDA initiative "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach."

The guidance was initiated in response to industry's request for a formal dispute resolution process to resolve differences related to scientific and technical issues that arise between investigators and pharmaceutical manufacturers during FDA inspections. In addition to encouraging manufacturers to use currently available dispute resolution processes, the guidance describes a formal two-tiered dispute resolution process that provides a mechanism for requesting review and decision on issues that arise during inspections.

The draft was published on September 5, 2003. In addition to the public comment period, the Agency conducted a pilot program with industry for a 12-month period. During that time, the agency received one Tier 1 request for dispute resolution and it was resolved. In addition, FDA met with representatives from industry trade associations in September 2004, near the end of the pilot period, to discuss the draft guidance and receive input.

Most of the changes to the guidance were made to clarify statements in the draft guidance. The following changes in the final guidance are noteworthy: (1) The time period for manufacturers to ask for clarification of a disputed scientific or technical issue was extended from 10 to 30 days; (2) if a request for formal dispute resolution reaches the agency's Dispute Resolution Panel and is considered appropriate for review, the panel will schedule a meeting to discuss the issue within 90 days of the request instead of the indefinite time period indicated in the draft guidance; (3) the guidance directs manufacturers to the Center for Devices and Radiological Health for disputes involving combination products when medical device components are the focus of the dispute, but clarifies that disputes solely involving medical devices are outside the scope of this guidance; and (4) the guidance clarifies that, during the dispute resolution process, a manufacturer may include relevant information that was not presented during the inspection, if FDA determines that a reasonable explanation was given on why the information was not presented during the inspection.

FDA Publishes Draft Vet Impurities Guide

FDA published a draft revised guidance called, *Impurities in New Veterinary Medicinal Products*, a Veterinary International Conference on Harmonisation (VICH) document. The draft revised guidance is a revision of a final guidance on the same topic for which a notice of availability was published in the *Federal Register* of July 7, 2000. The draft revised guidance clarifies the 2000 guidance, adds information, and provides consistency with more recently published VICH guidances.

The draft guidance has been revised to add information to certain sections and to provide clarification to other sections of the previous guidance. In addition, the guidance was updated to reference, where appropriate, other more recently published VICH guidances relevant to this topic. Finally, minor editorial changes were made to improve the clarity and consistency of the document. Public comments are due by Feb. 9 to ensure their adequate consideration in preparation of the final guidance document.

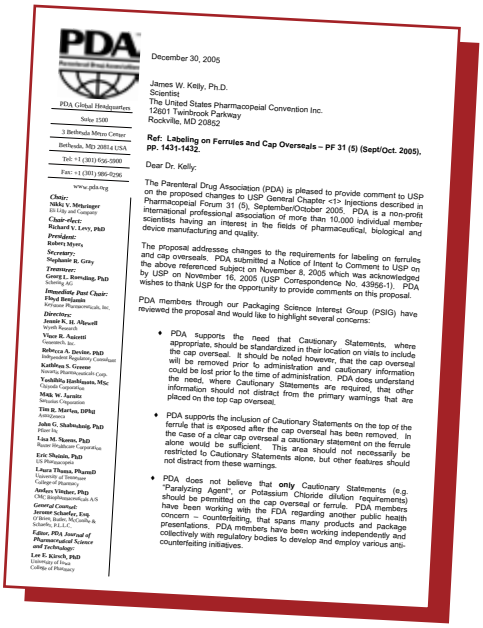
FDA Maps Out Centennial Celebration

FDA dates its origin to June 1906, when President Teddy Roosevelt signed the Food and Drugs Act and entrusted implementation of this law to the Bureau of Chemistry of the U.S. Department of Agriculture. The Bureau, the oldest U.S. consumer protection office, eventually became the FDA, an agency of the Department of Health and Human Services.

FDA has launched a special website at www.fda.gov/centennial with more information on the celebration. The centennial celebrations have the following aims:

- Observe FDA's role—past, present, and future—in protecting and promoting the health of the public, both in the United States and world-wide
- Inspire future efforts to advance science, innovation, and public health through partnerships and alliances with key FDA stakeholders
- Attract new generations of regulatory scientists
- Salute the contributions of FDA employees, alumni, legislators, academicians, industry, consumer groups and public health leaders to fulfilling FDA's mission

PDA Comments on USP General Chapter <1>



December 30, 2005

James W. Kelly, Ph.D.
Scientist, The United States Pharmacopeial Convention Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

Ref: Labeling on Ferrules and Cap Overseals – PF 31 (5) (Sept/Oct. 2005), pp. 1431-1432.

Dear Dr. Kelly:

The Parenteral Drug Association (PDA) is pleased to provide comment to USP on the proposed changes to USP General Chapter <1> Injections described in Pharmacopeial Forum 31 (5), September/October 2005. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological and device manufacturing and quality.

The proposal addresses changes to the requirements for labeling on ferrules and cap overseals. PDA submitted a Notice of Intent to Comment to USP on the above referenced subject on November 8, 2005 which was acknowledged by USP on November 16, 2005 (USP Correspondence No. 43956-1). PDA wishes to thank USP for the opportunity to provide comments on this proposal.

PDA members through our Packaging Science Interest Group (PSIG) have reviewed the proposal and would like to highlight several concerns:

- PDA supports the need that Cautionary Statements, where appropriate, should be standardized in their location on vials to include the cap overseal. It should be noted however, that the cap overseal will be removed prior to administration and cautionary information could be lost prior to the time of administration. PDA does understand the need, where Cautionary Statements are required, that other information should not distract from the primary warnings that are placed on the top cap overseal.
- PDA supports the inclusion of Cautionary Statements on the top of the ferrule that is exposed after the cap overseal has been removed. In the case of a clear cap overseal a cautionary statement on the ferrule alone would be sufficient. This area should not necessarily be restricted to Cautionary Statements alone, but other features should not distract from these warnings.
- PDA does not believe that only Cautionary Statements (e.g. "Paralyzing Agent", or Potassium Chloride dilution requirements) should be permitted on the cap overseal or ferrule. PDA members have been working with the FDA regarding another public health concern – counterfeiting, that spans many products and package presentations. PDA members have been working independently and collectively with regulatory bodies to develop and employ various anti-counterfeiting initiatives.
- Many of the anti-counterfeiting initiatives have focused on inclusion of both overt and covert features on injectable products. Pharmaceutical companies utilize the inclusion of anti-counterfeiting features into product package configurations to provide consumers with confidence that the product(s) they receive are from legitimate sources. Application of anti-counterfeiting technology should be considered a significant contribution by manufacturers toward prevention of this serious threat to patient health and safety. Anti-counterfeiting initiatives play a critical role in support of patient safety. Where Cautionary Statements are needed, PDA agrees that anti-counterfeiting features should not distract from the primary warning....

The complete comments letter is available at www.pda.org.

Sincerely,

Robert B. Myers
President, PDA

Israel Chapter Hosts Annual Meeting

Karen Ginsbury, PCI Pharmaceutical Consulting Ltd.

On December 27, 2005, the PDA Israel Chapter held its annual meeting at the Dan Panorama Hotel, Tel Aviv. Attended by 200 delegates, the meeting began with the president's and treasurer's reports for 2005.

We were fortunate to have **Gail Sherman** from TRI join us at the meeting. She made a presentation on "Worldwide Education and Training" at PDA to familiarize Chapter members with the educational services provided by PDA [**Editor's Note:** In this issue of the *PDA Letter*, Gail discusses the important role PDA Chapters play in helping to shape TRI's education agenda. Please see p. 33.**]**

Giora Shalgi, former CEO of Rafael Military Industries, gave a fascinating presentation on the topic of "Quality and Excellence as Milestones to Daring and Innovation." He explained how an industry that was losing money and customers managed a complete turnaround when senior management understood that quality was the tipping point. Using quality teams with regular input from the highest level of management, the company achieved profitability and gained an edge over worldwide competitors. Clearly, in today's competitive environment, we in the pharmaceutical and health care industry can learn from quality experiences in other industries.

After a Chanukah candle-lighting ceremony and a refreshment break, the meeting broke up into a series of roundtable discussions. The first sessions included:

- Method Qualification by Phase of Drug Development
- Process Development
- Vendor Qualification
- Life Cycle of IT Systems

These lively and highly interactive discussions left participants hungry for additional information and provided the Chapter executives with clues as to activities for the coming year. The second sessions were led by members of the Israeli Ministry of Health:

- **Rami Kariv**, PhD, GMP National Supervisor, on inspection issues
- **Mimi Kaplan**, PhD, Pharmaceutical Industry Laboratory Supervisor, on product registration
- **Ofra Axelrod**, PhD, Biological Products Unit Manager, on biotechnology issues

Once again the sessions were lively with audience participation, questions and answers and only the promise of a tasty supper managed to finally persuade participants to leave the conference rooms and enter the main ballroom for the evening's final portion.

Thanks are due (as usual) to all those who contributed to the success of the evening and, of course, to Forum–Biolog for all the logistical arrangements and the wonderful catering they arranged, as well as to the exhibitors who joined in making the evening a success.

(l-r) Israel Chapter President Sigalit Portnoy, Taro Pharmaceutical and Karen Ginsbury, PCI Pharma. Consulting

Israel Chapter VP Raphael Bar, PhD, Pharmos Limited with Gail Sherman, PDA

Member Leadership Opportunities

Exciting Breakthroughs in Nanotechnology are Happening...

PDA is seeking a member volunteer based in the United States, who is interested in contributing to and/or learning more about the exciting science of nanotechnology as it is being used in pharmaceutical and biopharmaceutical development and production. The volunteer will interact with the European Branch of the PDA Nanotechnology Interest Group. If you are interested in this unique *Career-Long Learning*℠ opportunity, contact Iris Rice, Coordinator, Regulatory Affairs and Science, at +1 (301) 656-5900 or rice@pda.org.

Explore the Emerging Technology of Disposable Manufacturing

The use of disposable purification devices and manufacturing systems is increasing, and with this, the need for scientific guidance for its application in pharmaceutical and biotech industries. PDA is forming a working group on Disposable Manufacturing—Technology and Regulation to create a comprehensive PDA program of knowledge capture (e.g., define industry trends using survey tools) and transfer (e.g., technical bulletins and reports, meetings and training) focused on this emerging manufacturing technology. Participants on the working group should include, but not be limited to, technology providers, industry users and regulatory champions (from industry and agencies). Global participation is encouraged. This is a great opportunity to be part of an interdisciplinary team exploring a recently emerging industry trend.

To join this working group, contact **Iris Rice**, Coordinator, Regulatory Affairs and Science, at +1 (301) 656-5900 or rice@pda.org.

Contribute to a Highly-Valued Industry Guidance: Help Write a PDA Technical Report

By joining a PDA Task Force, you will:

1.) Contribute to the development or revision of a highly-valued industry guidance

2.) Have an opportunity to collaborate with a team of subject-matter experts from industry, academic and government.

PDA Technical Reports are unique PDA products that offer expert guidance and opinions on a variety of important scientific and regulatory topics pertaining to pharmaceutical and biopharmaceutical production. Each document is put through the PDA peer review process—including review and approval by PDA's Science Advisory Board and Board of Directors—before they are published.

- **Revision of TR#14:** Industry Perspective on the Validation of Column-Based Separation Processes for the Purification of Proteins. The Task Force is looking for additional volunteers. Most Task Force work will be done via e-mail and regular teleconferences. The expected duration of the project is approximately six months to one year.
- **Revision of TR#15:** Industrial Perspective on Validation of Tangential Flow Filtration in Biopharmaceutical Applications. The mission is to update the technical report by describing current validation practices for TFF. Volunteers should work for biopharmaceutical companies in the areas of process validation and process development. Representatives from suppliers of TFF equipment and membranes are also welcomed. The Task Force will have regularly scheduled teleconferences of one to two hours.
- **Revision of TR#26:** Sterilizing Filtration of Liquids. TR#26 has proven to be a valuable tool in the application of sterilizing filtration in liquid aseptic processing. Recently, there has been considerable interest in updating the content of TR#26 to reflect changes in the industry since 1998. Team members will determine the areas of the document requiring revision in light of changes in practice and technology. Members will also consider topics to add to the document, such as the filtration of non-aqueous products, on-line, pre-integrity testing, redundant filtration and alignment of the document with current regulatory guidance, e.g., FDA's Aseptic Guideline. The first meeting is expected to occur in February. The Task Force will be lead by Paul Stinavage of Pfizer.

To volunteer to join any of the Task Forces, contact **Iris Rice**, Coordinator, Regulatory Affairs and Science, at +1 (301) 656-5900 or rice@pda.org.

Chapter Contacts

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

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E-mail:
greg.jordan@signet.com.au

India Chapter
Contact: Darshan Makhey, PhD
E-mail:
dmakhey@hotmail.com

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Q&A: Dialogue from the 2005 PDA Aseptic Processing Workshop

The following dialogue is from the Nov. 3-4 Aseptic Processing Guidance Workshop in Las Vegas, Nevada. This portion comes from a Q&A session on the second day of the workshop. Answering audience questions are: Kristen Evans, Guidance and Policy Team, Office of Compliance, CDER, U.S. FDA; John Grazal, Sr. Director, International Compliance Group, AstraZeneca; Terry Munson, VP, Pharmaceutical Manufacturing, Quality and Compliance, PAREXEL Consulting; Martin Van Trieste, VP, Worldwide Quality, Bayer - Biologics; PDA created the transcript following the conference.

"Could you please explain the difference between filter leak testing and efficiency testing, and what is the importance of efficiency testing?"

John Grazal: The FDA aseptic processing guidance goes into a fair amount of description of these two types of tests. The efficiency test is a test that is done by a HEPA filter manufacturer to rate the filter. And that involves basically challenging with a nominal monodispersed 0.3 micrometer sized challenge to determine the efficiency rating, 99.997, 99.999, etc. The integrity test that we perform is using an aerosol with a defined polydispersed particulate challenge, including, but not pinpointing, a 0.3 micrometer size. We challenge with an aerosol containing a preponderance of particles in the micron range, but not monodispersed at 0.3 micrometers….So the important thing is we don't do in the industry the efficiency test—that is done by the HEPA filter manufacturer.

"Is resterilization of glassware still acceptable to FDA?"

Terry Munson: I think it still is, as long as you have data that demonstrates that resterilizing the glassware doesn't change its characteristics. Again, that is going to depend on the type of glass used. If you were filling into something like flint glass, that could be a real problem, because the more you sterilize, the more you extract out of the glass, so you need to assess that against the potential effect on the product. Resterilization of glassware in and of itself is not that much of an issue, but you do need data to demonstrate that it doesn't have an impact on the specific product in question. So you would include that as part of a stability program.

"Adverse trend in personnel monitoring ultimately leads to the reassignment of the individual. How long do you reassign him?"

Martin Van Trieste: Until they are requalified. That could be the next week, the next month, whenever you choose to do it. Unless it is a chronic person who is having qualification issues, and then it is forever. I would never bring him back.

Kris Evans: Yeah, I think when they said reassigned, they [meant that the individual is already out. It is hard to say, unless something dramatically changes, that once they are out, they should come back in. The qualification and the initial testing are only going to tell you so much, but for whatever reason, this individual had already passed, because they were allowed in once. But ongoing data collection, or performance observation, or whatever, suggests that it is just an inappropriate job for them. And that happens. And firms need to tell operators ahead of time that this may happen to you, and that is just the way it is. Unfortunately, it becomes an issue to try and reassign people if they didn't know ahead of time that was a potential consequence of their job performance, or not even performance, it is just their own being—they are a shedder.

"What is FDA's stance on averaging EM data for monitoring one shift of critical samples, i.e., averaging on garments to achieve <1?"

Martin Van Trieste: The EMEA Annex 1 kind of says you can average the data....It insinuates that.

Evans: [As we worked on the Aseptic Guidance, we talked with our counterparts in the EU] and we discussed averaging. It is my understanding that they didn't actually mean to say that you could average samples per person or per shift or per location or line to come up with the less than one count. They actually meant to say what we are trying to say [in our guidance] and has also caused some confusion—samples in the critical area should normally yield no contamination. We were putting forth that concept. You have these action levels and it is <1 meaning, really, we don't expect to routinely find contamination there. . .And certainly, I think our guidance is pretty clear about averaging. It is not something that we expect to see, especially if it comes into the area of trying to dilute out what otherwise would be a very critical individual observation. It [averaging] may be a way of some additional type of trending or fulfilling a different objective of the state of control of the room, but we do expect individual values to be assessed per an action alert level. ➤

"Would mold be included in the criteria for surfaces or air for ISO 7 or Class 10,000, or would the criteria for those areas be 0 CFU for mold recovery?"

Evans: We don't differentiate in the guidance between bacteria and mold. But once mold starts creeping in, even in these ancillary or supporting areas, it is something to be dealt with and taken seriously. And oftentimes, a lot of the environmental monitoring programs aren't specific for mold. So if you start to pick it up in your standard environmental monitoring, perhaps it is time to make sure you are doing more specific monitoring for mold and making sure it is not getting out of control.

"Should the operator regown after their gown has been sampled, or is wiping with an alcohol wipe okay? Also, is there some time limit recommendation for operators to change their gowns?"

Grazal: We also had a question around fingertip monitoring, the same kind of concept: Is it appropriate to sanitize the gloves after monitoring during the manufacturing process or must the gloves be changed? Certainly, the aseptic processing guidance is not specific on this, but my view in both of those instances, we would want to change the gown and change the gloves. It is too much of a risk to have that kind of proximity, and whether you sanitize, if you get all the media off or if you don't, I don't want media proximal to my operation. So I would recommend a change, if you are doing that monitoring during the actual process.

Van Trieste: I see people nodding. I think there is consensus on the panel on that discussion.

"Can you give some guidance on the FDA's definition on 'routine monitoring' of personnel by supervisors and QA?"

Evans: Good question. We don't actually have a definition, to answer it literally. However, we emphasize that concept —and you obviously caught on to that—a couple of times in the guidance document. And that comes from experience more than anything else. A lot of us who wrote the guidance did many inspections, and we, as part of our inspections, basically spent a lot of time monitored what people were doing….

Go look—aseptic filling operations you must get out and observe. And I'm emphasizing that, because my experience in observing operations is that people just do [unexpected] things. You know, you may see the person do something that's objectionable; however, it really indicts a lot of things, a lot of systems, whether it is training, supervisory oversight, just GMP awareness of that operator (they should know better than to do those things). So we wanted to emphasize it in the guidance document. It is not defined, but we are encouraging it. You have to recognize that the true test of people, which are the biggest variables in these operations—is observation and verification that they are performing as intended. The question came up earlier, how well do you need to document that? It depends. This observation element should be considered a component of personnel qualification. Some type of observation program, in addition to data, becomes a requalification event. Therefore, I think that should be documented, because if it isn't documented, it kind of slips through the cracks or it doesn't necessarily happen….

Another thing about observation and documentation of it, is that media fills really do need to be representative of what is going on, what people are actually doing, not just what they are suppose to do. So there needs to be some system in place to observe and see what operators are doing and make sure that is within the realm of what you expect and want them to do, and also make sure our media fills are representative. If there are things that they do or have to do based on the layout or line design or ergonomics, has the firm adequately captured that in media fill programs. That doesn't mean a media fill program can qualify an otherwise unacceptable practice, but you need to have this link to make sure that media fills are representative of what happens in production…..

PDA's Aseptic Processing Guidance Workshop Series

PDA will continue its Aseptic Processing Guidance Workshop series in 2006, with a workshop planned for Prague, Czech Republic, in June. Members of the planning committee will once again provide expert insight into the FDA aseptic processing guidance, based on their many years working with PDA to help shape the final document. Watch for future updates on this conference in the PDA *Letter* and at www.pda.org. More dialogue from the 2005 series will be included in upcoming issues of the PDA *Letter*.

Photo Highlights from PDA's Fall Events

PDA Workshop on Viral Safety Evaluation of Biotech Products Used in Clinical Trials, Langen, Germany • Dec. 1, 2005

Prof. Dr. Cichutek of the Paul Ehrlich Instutue, welcomes the capacity attendance to the PDA Viral Safety Workshop.

Regulatory Framework and Industry Perspectives (seated l-r): Annemarie Möritz, Novartis; Michael Ruffing, Boehringer Ingleheim; Johannes Blümel, Paul Ehrlich Institute; Isabelle Sainte Marie, AFSSAPS; (standing l-r) Kurt Brorson, CDER, FDA; Ralf Gleixner, Serono; Yuling Li, Human Genome Sciences; Roland Günther, Novartis (Chair)

Aseptic Processing Guidance Workshop Las Vegas, Nevada • Nov. 3-4, 2005

Answering questions: (l-r) Martin Van Trieste, Bayer; Kristen Evans, U.S. FDA; John Grazal, AstraZeneca; Stephen Bellis, IVAX Pharma.

Validation strategies in downstream processing (front row l-r) Hannelore Willkommen, RBS Consulting; Qi Chen, Genentech; Sharlene Savino, Centocor (back row l-r) Pascal Valax, Serono; Gregory Blank, Genentech; Philippe Marschal, Novartis

Day 1 panel: (l-r) John Grazal, AstraZeneca; Martin Van Trieste, Bayer (standing); Terry Munson, PAREXEL Consulting; Harold Baseman, ValSource, LLP; Carol Lampe, Baxter Sterility Assurance

Workshop participants kept the exhibitors busy!

Agenda for the PDA/EMEA Joint Conference Takes Shape

PDA continues to make preparations for its first ever PDA/EMEA Joint Conference, to be held Oct. 12-13, 2006, at the Sheraton Park Lane Hotel in London. Preceding the conference and exhibition (Oct. 10-11), PDA's Training and Research Institute will offer two days of job-focused training courses on quality assurance, quality control, operations, management and training.

Focused on Understanding the European GMP Environment, the PDA/EMEA Joint Conference offers a unique opportunity to interact and network directly with the people who are leading current regulatory initiatives in the European Union. The conference will provide a forum to facilitate dialogue between top European health authorities and industry experts in an unbiased, science-based forum.

"This conference will have an unsurpassed representation of senior-level speakers and committee members from the European Commission, EMEA and eight national regulatory agencies," said conference co-chairs **Anders Vinther,** PhD (CMC Biopharmaceuticals, Denmark) and **Tim Marten** (AstraZeneca, UK). "For everyone involved in pharmaceutical/biopharmaceutical regulatory and quality matters this will be the event of the year in Europe."

Several top officials at the Euro-pean Medicines Agency and the European Union are already committed to speaking, including **Thomas Lönngren**, Executive Director, EMEA; **Martin Terberger**, Head of Pharmaceuticals Unit F2 of DG Enterprise; and **Emer Cooke**, Head of Sector Inspections, EMEA.

Educational sessions will cover key quality issues of relevance both in Europe and globally, including: a thorough introduction and discussion of the regulatory environment in Europe, inspections, implementation of EU regulations in the national member states, contractor management, counterfeiting, the role of the Qualified Person, investigational medicinal products, dedicated facilities, starting material and new technologies. In addition, PDA will host numerous networking events, including an exhibition hall featuring new, innovative technologies and services from vendors from around the world.

PDA/EMEA Joint Conference Preliminary Agenda

Thursday, Oct. 12, Morning
- Understanding the Regulatory Framework
- Legislation and How It is Made
- Regulatory Framework and Key Players
- Inspections and How They Occur
- European GMP Implementation in Member States

Thursday, Oct. 12, Afternoon
- Concurrent Session

Friday, Oct. 13, Morning
- Consistent Implementation of EU GMP
- Harmonized Legal Requirement and Guidance
- How Regulators Can Make the System Work
- How Industry Can Make the System Work

Friday, October 13, Afternoon
- Manufacturing and Inspections Past/Present/Future: Moving from a National to a Global Approach

For more information on this event, including the full program planning committee, visit: www.pda.org/pdaemea2006.

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Genentech's Susan Desmond-Hellmann, MD, to Give Keynote Address at 2006 PDA Annual Meeting

The confirmation of Susan Desmond-Hellmann as keynote speaker sets the tone for what is sure to be one of the best Annual Meetings in recent PDA history. Dr. Hellmann is the President of Product Development at Genentech. His responsibilities include regulatory affairs, development sciences and quality, as well as business development and strategic pipeline development. She joined Genentech in 1995 as a clinical scientist and was named Executive Vice President, Development and Product Operations in 1999, and later named chief medical officer. In addition to her work at Genentech, Hellmann is an adjunct associate professor of Epidemiology and Biostatistics at the University of California, San Francisco.

In 2004, Hellmann was named for the third time to *FORTUNE* magazine's "Top 50 Most Powerful Women in Business," and she was listed as one of *The Wall Street Journal*'s "Women to Watch." In 2002, she was named to the U.S. Department of Health and Human Services Advisory Committee on Regulatory Reform, and in 2001 she was named to the board of directors of the Biotechnology Industry Organization. Since 1980, Hellmann has received many honors and awards for her work in oncology and AIDS research.

The addition of Dr. Hellmann to the **2006 PDA Annual Meeting** agenda will bring the insight of one of industry's most prominent biotech business leaders to conference attendees. Her presentation will tie into this year's annual meeting theme — *Pharmaceutical Manufacturing Science in the 21st Century: From Innovation to Implementation.*

Managing Your Supply Chain: Temperature-Sensitive Products

Rafik H. Bishara, PhD, Chair, PDA Pharmaceutical Cold Chain Discussion Group

The global handling of temperature-sensitive products receives much attention from pharmaceutical manufacturers, regulatory agencies, pharmacopeias, academia and members of the supply chain to assure that the integrity of the product is not compromised before it reaches the patient. That's why it is essential for pharmaceutical, biopharmaceutical and supply-chain professionals to implement a cold chain management strategy that protects a product during all stages of production, including development, transportation and distribution.

By taking an in-depth look at the factors affecting the cold chain management of drugs, the **2006 PDA Pharmaceutical Cold Chain Management Conference** will provide guidance on how to effectively implement technologies and quality systems within regulatory requirements and public standards to guarantee the safety, efficacy and quality of the product. This two-day conference features eight plenary sessions designed to help pharmaceutical and biopharmaceutical professionals identify and implement successful cold chain management strategies:

- Pharmaceutical Cold Chain Discussion Group (PCCDG) and Technical Report No. 39: Learn about the first PDA Technical Report addressing cold chain issues.
- Global Regulatory Requirements: Implement a cold chain strategy in compliance with regulations and standards.
- Stability: Learn how to develop product stability information that is necessary to support cold chain activities.
- Validation and Qualification: Learn how to design study protocols that will lead to science-based conclusions.
- Distribution/Transportation: Implement programs that assure the integrity of the product in the supply chain.
- Fundamentals of Cold Chain Packaging: Learn about factors to consider when developing a cold chain package and container.
- Cold Chain Quality Standards: Review examples of quality systems that ensure proper documentation and oversight of cold chain products.
- Partners in Pharmaceutical Cold Chain Management: Learn about real-life cold chain solutions from partners in the supply chain.

This conference was planned by some of the same PDA members who drafted PDA Technical Report #39, and as such, offers participants unique insight into this important document.

For more information about the 2006 PDA Pharmaceutical Cold Chain Management Conference or to register, visit www.pda.org/coldchain2006.

Vice President's Message

Gail Sherman

TRI and the Chapters

I thought I would spend some time writing about the value of working with PDA's various Chapters in creating the best *Career-long Learning*SM courses in the industry.

When I attended my first PDA/FDA Joint Regulatory Conference as a PDA employee in 2004, I sat in the Chapter Council meeting looking for input and assistance in developing the TRI lecture course series for 2005. Following the meeting, I was left pondering how TRI and the Chapters could better work together; what could we do to support each other; and how TRI could support the needs of the members in the various Chapters' regions. At that point, I didn't fully understand the Chapters' role. After my next meeting with the Chapter Council at PDA's Annual Meeting in 2005, I had formed a much clearer picture of how important our relationship was. At that meeting, I heard many more questions about what TRI could do for the Chapters, including whether TRI would sponsor training at Chapter events.

I took this thought back to Baltimore and tried to figure out what we might be able to do. As fortune goes, I was cleaning out old files and found an old PDA document referencing how TRI and the Chapters could work together on developing and delivering joint training programs. It looked like an approach that could be of great benefit to both TRI and the Chapters, so I sent it to PDA's Chapter manager to see if this document could be resurrected. The document was updated and was posted on the PDA website.

Next, I decided to visit individual Chapters to build stronger ties between them and TRI. I concluded that, together, the Chapters and TRI could schedule courses relevant to the individuals and companies in each Chapter's region. My first trip was to the Southeast Chapter meeting in the spring of 2005. The result? We have scheduled 11 courses in Research Triangle Park, N.C. for March 2006, with course topics requested specifically by the Chapter.

My next move was to contact the Chapter presidents in the regions where we were planning to present course series during 2006. The input we received from the Midwest Chapter for the St. Louis Course Series, scheduled for August, is invaluable, and it is a promising start to the collaborations we are committed to pursuing this year as we plan the 2007 course series.

Another way TRI can serve the Chapters' needs is by hosting courses in conjunction with a Chapter meeting. For instance, this June, TRI will conduct courses in conjunction with the Canada Chapter Annual Meeting in Vancouver, B.C. Input on topics has been received from Chapter members, and TRI is scheduling the courses accordingly.

In December, I attended the Israel Chapter Annual Meeting *(see page 24)* and talked about the opportunity to expand TRI training globally. I met with several Chapter members about the possibility of providing training in Israel for pharmaceutical manufacturers and the health authority in the region. We will continue to have discussions on this option.

Chapter support can be provided in ways other than just training input. For example, when TRI needed a HEPA filter installed in the University of Basel facility for the TRI "Practical Aspects of Aseptic Processing" course, the Central European Chapter jumped in and contracted to have this done—at their expense. We certainly appreciated this effort.

Locally, I make the effort to attend the Capital Area Chapter and Delaware Valley Chapter meetings and will continue to do so as time permits. And, I would be happy to visit other Chapters that are interested in PDA training programs. We are presently researching venues for 2007, so if you have any suggestions, please let me know.

In closing, all of us at TRI look forward to continued opportunities with the Chapters, and we want to let you know how very much we value your input to PDA's education efforts. Please be in touch!

Kazakhstan Delegation Thanks PDA

The following is a translation of the remarks of Maria Kamanova, Kazakhstan Ministry of Health, and Raushan Turysbekova, National Center for Expert Review of Medical Products at the closing session of the TRI-Kazakhstan training, November 10, 2005. The following translation is based on the notes of the interpreter, and, though it closely reflects the essential meaning of the presentations, it should not be considered a verbatim copy of the original speech.

Maria Kamanova: On behalf of the whole delegation, I would like to say thank you, and to express our feelings of gratitude.

Our gratitude is connected also with the fact that the government and president of our country has initiated a program, which is to last through the year 2010, and whose goal is to improve the pharmaceutical industry of Kazakhstan—to bring it more into conformance with international practice and standards. It is clear that the training program in which we have just participated will help us to achieve this goal.

We hope, within the framework of this presidential initiative, to create within three years, both a governmental inspectorate as well as a cadre of trained inspectors….

We are also very happy that we had the chance to work with PDA. We saw in this program that you carefully took into consideration both our level of professional preparedness as well as the requests that we had made in advance.

It was particularly interesting that the program included presenters from differing perspectives: we had U.S. FDA regulators, people from the industry with hands-on experience and also private consultants. All the trainers made a big and very good impression on us, and it is very difficult to single out any particular one for special praise….

We will continue our training after we return home, and we hope that we will continue it also with PDA, either with return visits of our own, or with follow-on training programs for other groups. In any case, we have made a fine beginning.

Incidentally, there is an idea embedded in the slogan of PDA that we have seen repeated so many times—that PDA is "connecting people, science and regulation"—and our program here has shown that this is really true. We are all happy and proud that we can now call ourselves members of PDA. Maybe, at some point in the not-too-distant future, we will create a branch of PDA in Kazakhstan that will represent the entire Central Asian region.

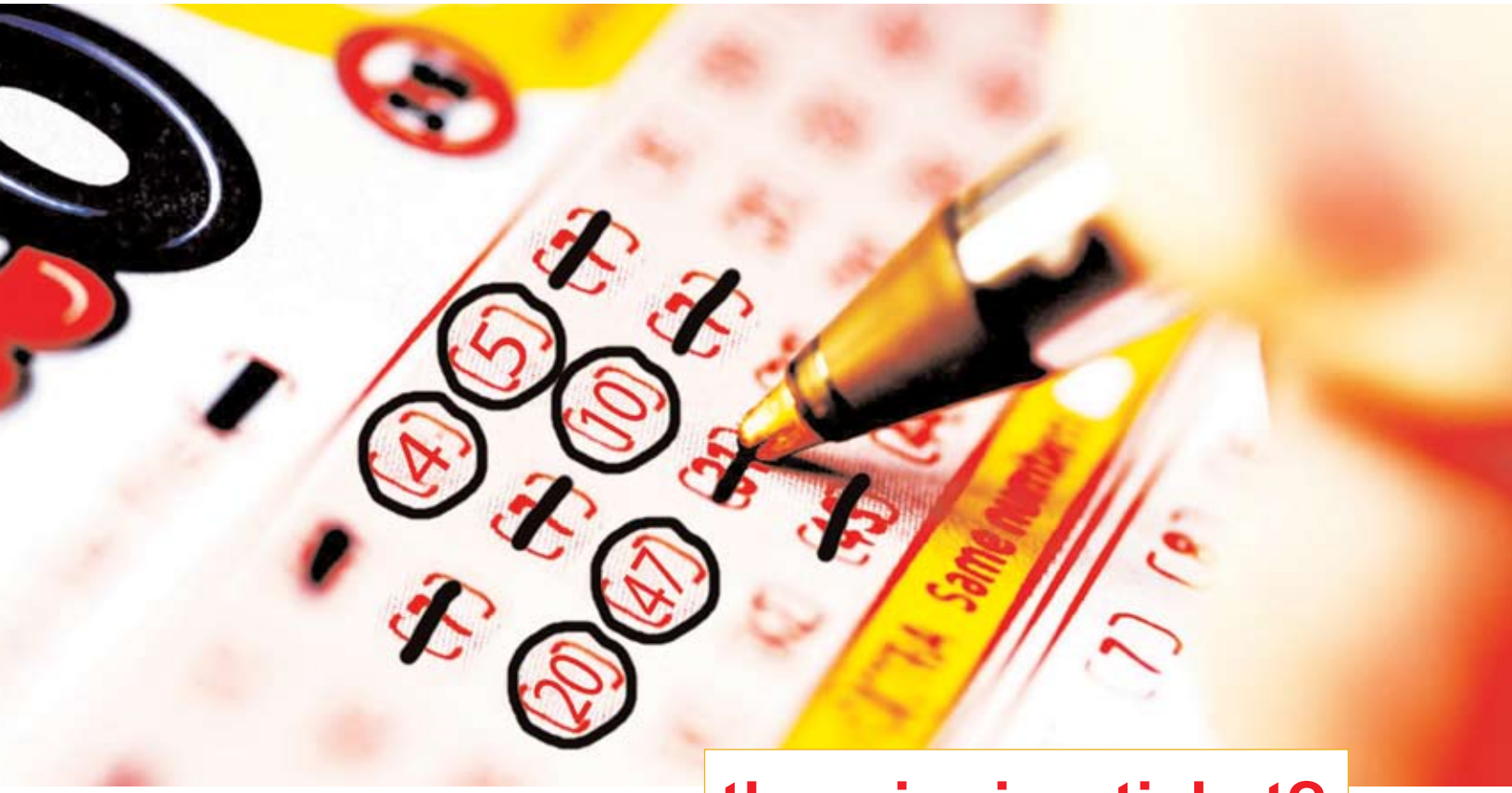
We would also like to thank Gail Sherman for all her care and work. With great diplomatic skill, kindness and efficiency she took good care of us, from hotels and transportation to cultural programs. The tour of D.C. that she put together for us was very well designed. She made a constant effort to pay attention to our needs, while bearing in mind the specifics of our culture—even making daily changes to our menu as necessary!...

Raushan Turysbekova: I would like, on behalf of the National Center for Expert Review of Medical Products, to also join my colleagues in expressing my thanks for this program. The National Center is also involved in the process of [regulating pharmaceuticals] in Kazakhstan. Upon returning home, each of us will be sure to brief our respective upper management on the many productive results of our visit.

Within the framework of the program for improving and modernizing the pharmaceutical industry in Kazakhstan, we intend to carry out our work within our country in [approximately] the following form. We will have a number of areas of specialization, such as the production of biologics, medical instruments and equipment, and so forth. On the regulatory side, we will also be developing regulations, criteria for acceptance of applications, tests, quality control procedures, and we will also have regulatory groups who are focused on each of the specialized medical or pharmaceutical areas. It would be great if we could try to keep in close coordination, so that future training programs will match our own organizational development as it evolves.

Thank you also for today's lectures, which indeed presented answers to questions that we had posed earlier, albeit within the limitations imposed by the amount of time left....

Prepared by interpreter
Paul Grenier, Nov. 10, 2005



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