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PDA Letter

July/August 2010

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PDA Remembers Raymond Shaw

Chris Smalley, Merck

On Tuesday, May 25th, we lost **Ray Shaw**. Not only his family and friends, but the entire PDA community and industry lost a real leader and great scientist when Ray was doing one of the things he enjoyed best, fishing in a lake near his home in Pennsylvania. His kayak was found in the middle of the lake on Wednesday with his fishing gear still inside. He was later recovered.

Many of you knew Ray from his career at Merck, working with him at Wyeth or from his years of service to the PDA, including serving as Chair from 1996 to 1997.

Following graduate school at the University of Connecticut, Ray joined Merck in 1976. He worked in the biological process improvement area where he supported blood products and bacterial vaccines. He became the Manager of the biological quality laboratories for all of Merck's vaccines, biologics and sterile pharmaceuticals business around the world. Ray continued to hone his expertise in the vaccines area and took part in the initial technical transfers of several of the viral and bacterial vaccines. He was very proud of his work on the Hepatitis B vaccine, as well as anti-venom products. Ray became as well known for his expertise in process validation as for his deep, booming voice.

In 1995, Ray joined Wyeth Pharmaceuticals as Vice President of Quality for the Parental Manufacturing Operations. He was instrumental in the integration of Lederle Pharmaceutical and Wyeth. As the vaccine and biotech business grew at Wyeth with the development of pneumococcal vaccines and the acquisition of the Genetics Institute, he was named Vice President of Quality Control for Wyeth's Vaccines and Biopharmaceutical Manufacturing Operations.

Ray had always been a contributor to the Parenteral Drug Association and was recognized as a strong technical leader and served as president in 1996-1997. He was always ready to share what he'd learned over the years and give guidance without lecturing—he never talked down to anyone. Known to everyone as a kind and gentle man with a warm heart, he was well respected by those who worked with him for having a wealth of knowledge for biological products production, quality and regulations. A nickname he acquired was "Reg Man," because whenever someone

continued on page 6

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Cover art:
Aseptic processing and sterile drug manufacturing involve increased vigilance to guard against contamination. High-profile troubles at three large manufacturers recently underscore the difficulty involved.

Coming Next Issue:
Preparing for a Regulatory Inspection

Editor's Message

What Would Carleton and Shaw Think?

Following the shocking news that **Frederick Carleton** passed away, we learned about **Raymond Shaw**. It is sad that two of our past leaders have gone in such quick succession.

When I look at the feature story we chose to write for this issue, I wonder what Ray and Fred would have said about the problems with aseptic processing found by the U.S. FDA at three large manufacturers. Ray might have suggested that these companies focus more resources on employee training. Fred might have advised more guidance from the Agency and more action by our community to develop new technical reports to further help manufacturers. Whatever their response, one thing is certain, both would have believed that PDA could and should be ever vigilant in offering the products and services to help our members meet the regulatory and scientific challenges associated with aseptic processing.

So these two giants of PDA have passed, but we continue to bear the torch for PDA. In this issue, we carry on our recent tradition of dedicating our first of two annual "double" issues to PDA's bread and butter, sterile products and aseptic processing. The aforementioned feature article takes a look at the recent troubles at Genzyme, Teva and Hospira. Our purpose is not to point fingers or play "gotcha" journalism with three companies that have many members in our community. We believe it is instructive to look at the specific problems so other companies can try to avoid similar difficulties. In addition, we are not implying that the aseptic guidance is inadequate or not useful by comparing the deviations to chapters in the guidance. Rather, we wonder if the current state of regulatory actions signify the need for new guidance.

This issue also previews many of the sessions and activities at the upcoming PDA/FDA Joint Regulatory Conference. It is an important meeting that allows the industry segment our community to interact with the regulatory segment. This forum certainly falls within the traditions set by our past leaders, Shaw and Carleton. We hope they are proud.

PDA Letter

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Raymond Shaw: A Man of Many Roles

Excerpts from an interview with Raymond Shaw, conducted by PDA staffer Trish Rafferty and published in the June 1996 *PDA Letter*

How did you first become involved with PDA?

I started teaching courses on the "Principles of Sterilization" and "Sterilization–in–Place" in the mid-eighties. I also became active in the microbiology committee. These were my areas of interest in both education and experience in the pharmaceutical industry. I got to meet lots of colleagues with whom I could share questions, thoughts and vice versa. The networking was phenomenal.

I never knew that you taught for PDA. Is that something you enjoy?

I enjoy teaching; I have always enjoyed it. I have done it within the PDA and within manufacturing companies. While working for Merck, I provided a number of training courses. Now I am starting a similar program within Wyeth-Ayerst. If you have an expertise, I think sharing it is important.

I always seem to get more out of a course than I put into it. If more people realized that, more people would teach. You are providing information, but you also get feedback. You will learn about new problems especially if you allow opportunities for participants to discuss a particular problem that they have encountered in their own work. Most of the courses, in fact all of the courses, I have ever taught have repeated many of the more unique examples brought up in the classroom. It makes the material more real, and the students can relate to it more.

[Editor's Note: Click here for a complete PDF of the article.**]**


PDA LETTER

Chairman on Future of Association

Plans for Specifications Conference Continue to Take Shape

Deadlines

Features

PDA Remembers Raymond Shaw, continued from cover

thought that there was a regulation addressing an issues but couldn't find it, they would call Ray and he would frequently be able to cite the CFR reference immediately.

Ray had a deep love of the outdoors, and enjoyed hunting and fishing with his sons, Burr and Hunter, at Peace Valley Park and the Poconos in Pa., the Jersey shore, Vermont and Maine. He would regale many of us with his stories of hunting and fishing; with his frequent extended visits to the Wyeth facilities in Sanford and Marietta, he would travel with his tackle so he could sample the local fishing spots. Whenever possible, he'd stay in a hotel with suites so he could cook what he caught! Ray hunted more species of animals than most people can imagine, ranging from squirrels and deer to rattlesnakes.

We will all miss him, his knowledge, his warmth and his stories. Good hunting and fishing Ray!

Honoring Ray

Memorial contributions in Ray's name may be made to:

Bucks County Hero's Scholarship Fund
1760 South Easton Road
Doylestown, PA 18901

North Penn Goodwill Service, Inc., (Emergency Canteen Service)
Box 64251
Souderton, PA 18964

The Reed and Steinbach Funeral Home, located in Doylestown, Pa., will also forward on any donations they receive in Ray's name.

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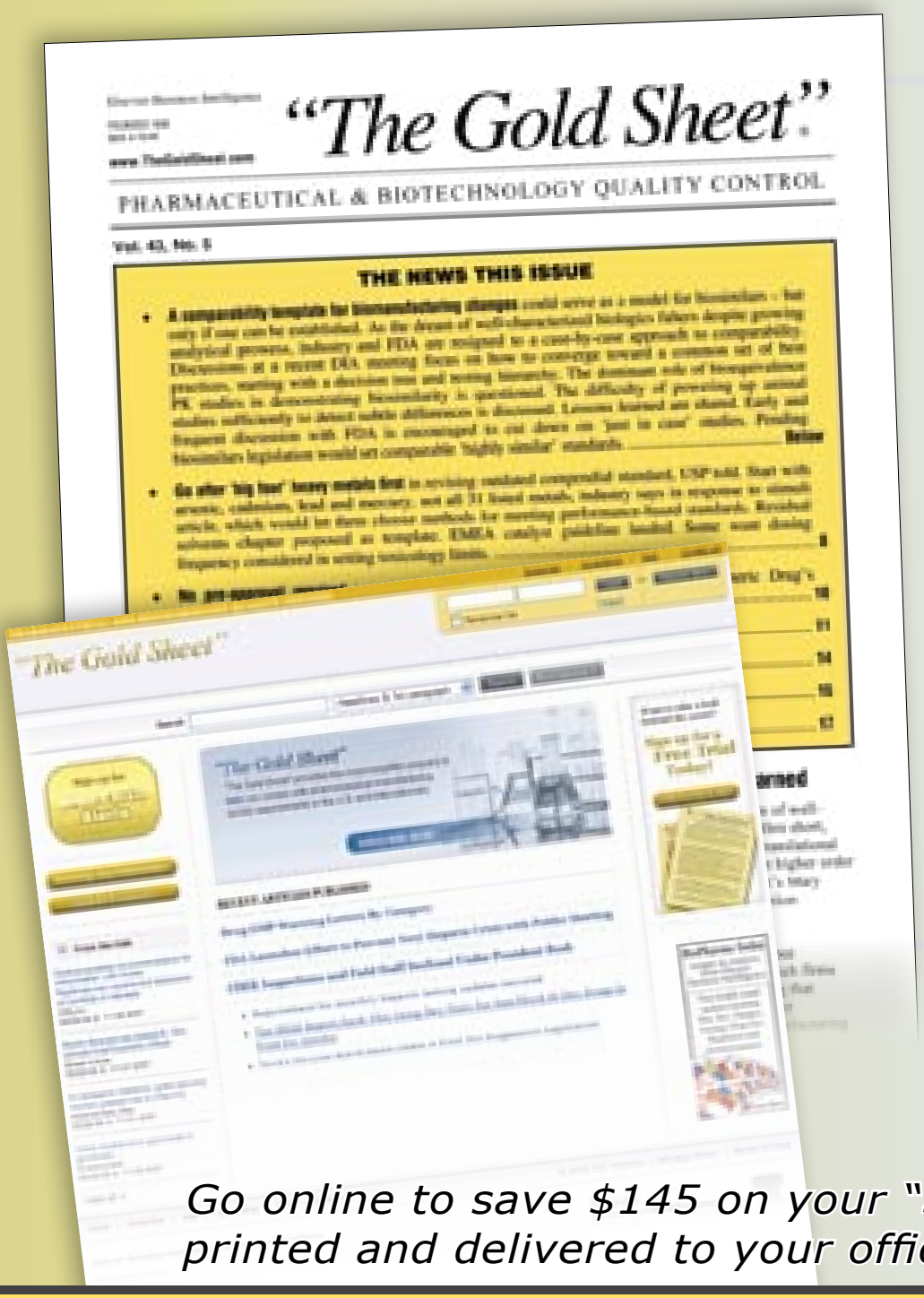

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Science & Technology *Snapshot*

Advisory Board *Watch*

An Inside Glimpse of the BioAB

For three years, **Soren Thuesen Pedersen** has served as a volunteer on PDA's Biotechnology Advisory Board (BioAB), a group that identifies biotechnology issues of interest to PDA members globally.

Soren, a Director of External Affairs at Novo Nordisk, has been in the biopharma field for 22 years. He joined the BioAB after hearing about it from a colleague and receiving a formal invitation to join the group from then co-chairs **Norbert Hentschel** and **Gail Sofer** in 2007.

The *PDA Letter* talked to Soren about his experience so far on BioAB.

PDA Letter: What motivated you to join the BioAB?

Soren: As a representative of a biotech company, I see a clear need for having such a forum within the biotech arena. We traditionally focus on the solid dosage forms area or classical parenterals. It is important to be able to discuss scientific biotech matters across the Atlantic, provide high quality input to legislators on new guides and guidelines, and also set standards ourselves with technical reports.

PDA Letter: How have you benefitted professionally and personally from your activity on the BioAB?

Soren: It's an excellent networking opportunity, and we have used the work for developing internal positions for various fields within scope of the Biotechnology Advisory Board. It gives leverage to my professional work, and strong focus is given in the United States to biotech issues, which is a big focus in my company.

PDA Letter: BioAB has had an auspicious start; since its inception in 2005, the BioAB has contributed to the advancement of PDA's Process Change Management Operations (PCMO) initiative; developed 19 new task forces and numerous technical reports. In addition, it has facilitated multiple training opportunities, workshops and discussions. Do you think it will be able to continue its momentum?

Soren: Yes, but we might need to focus on high-impact areas of interest. Many participants do this as an add-on to their daily work, so resources can be limited.

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Technical Report *Watch*

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

- *Technical Report No. 22: Process Simulation Testing for Aseptically Filled Products* **(BoD)**
- *Biological Indicators for Gas and Vapor-Phase Decontamination Processes: Specification, Manufacture, Control and Use* **(BoD)**
- *Technical Report No. 3: Validation of Dry Heat Processes Used for Sterilization and Depyrogenation* **(BoD)**
- *Technical Report No. 13: Fundamentals of Environmental Monitoring* **(SAB)**

In Publication: TR is approved and ready for publication.

- *Technical Report No. 50: Alternative Methods for Mycoplasma Testing*

Task Force *Corner*

[Editor's Note: In this edition of Task Force Corner, two check in—the Glass Task Force and the GMPs for Investigational New Drugs (starting on page 11).**]**

Glass TF Adds Ampoules, Cartridges & Syringes to TR

Nicholas R. DeBello, Wheaton Industries and Michael Eakins, Eakins & Associates

A glass task force under the direction of the PDA was formed in 2003 for the purpose of creating a technical report that would provide consistent, standardized quality criteria that could be used by pharmaceutical companies for the visual inspection of incoming glass containers such as molded glass bottles and tubular vials. The completion of this project occurred in 2007 when *PDA Technical Report No. 43, Identification and Classification of Nonconformities in Molded and Tubular Glass Containers for Pharmaceutical Manufacturing* was published. The report contained a description of the nonconformity, its location and classification. A photograph or drawing of each of the nonconformities was also supplied in an accompanying lexicon.

When TR-43 was being developed, a decision was taken to limit its scope to molded glass bottles and tubular vials only while recognizing that this approach ignored other tubular glass containers namely ampoules, cartridges and syringes. Following publication of TR-43, a decision was made to create a new glass task force with **Michael Eakins**, Principal Consultant, Eakins & Associates, and **Nick DeBello**, Director, Quality Management Systems, QMS, Wheaton Industries, as Co-chairs for the sole purpose of developing these new lexicons. Members, for this international task force, who had familiarity with these products were assem-

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2010 PDA/FDA Joint Regulatory Meeting *Preview*

IGs, ABs, TFs and PCMO to Meet at PDA/FDA

PDA members and volunteers will dedicate some of their time at the *2010 PDA/FDA Joint Regulatory Meeting* conducting the business of the Association. All participants at the PDA/FDA meeting are welcome to participate in interest group discussions.

Sunday, September 12:

- **Analytical Methods Development Task Force (TF):** 1:00 p.m. – 5:00 p.m.
- **Facilities and Engineering IG:** 4:00 p.m. – 5:00 p.m.

Monday, September 13:

- **Biotechnology Advisory Board:** 11:30 a.m. – 2:30 p.m.
- **PCMO Q01, Capture Knowledge Management:** Noon – 1:00 p.m.
- Concurrent IG sessions: 4:30p.m. – 6:00 p.m.
  - **Prefilled Syringe**
  - **Sterile Processing/Lyophilization**
  - **Clinical Trial Materials**
  - **Process Validation**

Tuesday, September 14:

- **PCMO R01a, Quality Risk Management & Biotechnology Manufactured APIs:** 12:15 p.m. – 1: 15 p.m.
- **Science Advisory Board:** 12:15 p.m. – 2:30 p.m.
- **PCMO RO1, Risk-Based Manufacuring:** 12:15 p.m. – 4:15 p.m

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Journal *Preview*

Sterile Product Processes, Methods Examined

Journal Associate Editor **Anurag Rathore** analyzes the progress made in bringing biosimilars to market in Europe and the United States in the July/August issue's editorial.

Apropos with the July/August issue of the *PDA Letter*, the July/August Journal also contains several articles on sterile products manufacturing, including research into the use of moist heat disinfection for HBV and the use of radiation sterilization for aseptically produced products. An technology/application article compares the limit of detection for a rapid micro method and the USP method.

Editorial

Anurag Rathore, "Biosimilars"

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In *Print*

Risk Assessments for Environmental Monitoring

The following is excerpted from the chapter, "Dealing with Contamination: What is the Risk to the Product?" by Jeanne Moldenhauer, Excellent Pharma Consulting. The chapter appears in the recently published PDA/DHI book, Environmental Monitoring: A Comprehensive Handbook*, Vol. 4, edited by Moldenhauer.*

In recent years there have been some presentations given on performing risk assessments in conjunction with potential contamination present when manufacturing non-sterile pharmaceuticals. Dr. Guilfoyle presented a method for risk assessment that he used as part of the FDA's investigation of non-sterile products that were potentially contaminated. In this presentation he said, "The presence of a wide variety of *opportunistic pathogens* or even non-pathogenic environmental

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Advisory Board Watch, continued from page 8

PDA Letter: Prioritization of the various technical report projects in the pipeline is another pressing course of action. Is there any progress being made?

Soren: Yes, but improvements can be made. Again, we need to focus and make sure that the things we start are of value, get completed on time and provide worth to members in due time. Given the make up of the group and the practical issue of the time difference, we need to make sure decisions are made efficiently. Consensus is not always an option if people can't make meetings. *Clear ground rules for management and governance are important!

PDA Letter: What would you say to someone looking to join the BioAB?

Soren: Bring your enthusiasm, professionalism, scientific and cultural curiosity with you, and we'll extend a warm welcome to you!

* PDA tries to reach a consensus by polling members of the AB in all cases

Task Force Corner, continued from page 9

bled. These included consultants; leading glass manufacturers and converters; and pharmaceutical representatives totaling about 30 members in all.

The scope of this new glass task force was to develop a lexicon of attributable defects for glass ampoules, cartridges and syringes that would visually illustrate nonconformities, their definition, location and classification for disposition. Like TR-43, this new document would be a consensus-based nomenclature providing consistent and standardized quality criteria. The document would not be a standard but a guideline for the most frequently found nonconformities associated with these products.

The Task Force has been in place now for almost two years. During this time three sub groups have been created to address the three new lexicons:

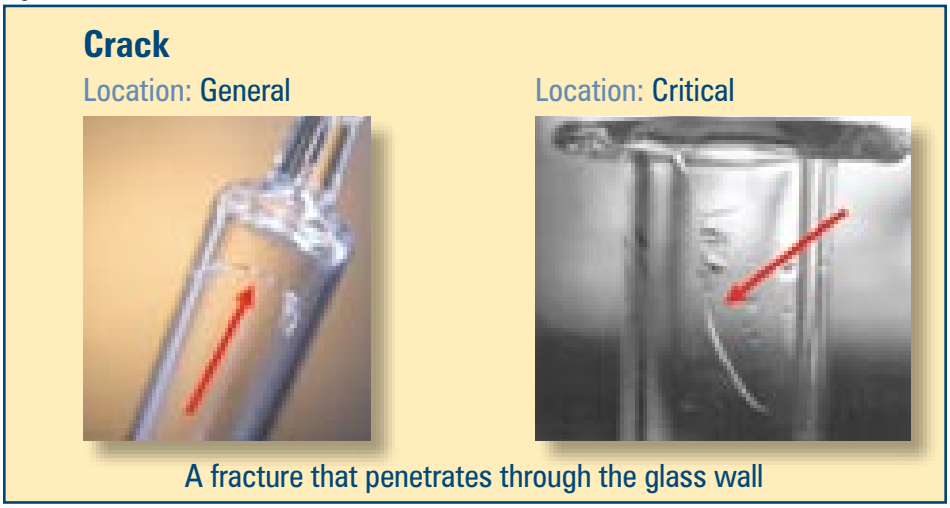
- Ampoules – Chaired by **Nicholas DeBello**
- Cartridges – Co-chaired by **Mads Espersen**, Principal Scientist, QA Packaging Materials, Novo Nordisk and **Nick DeBello**
- Syringes – Chaired by **Roger Asselta**, Vice President, Technical Affairs, Genesis Packaging Technologies

Each new lexicon has been created listing approximately 45 commonly found nonconformities. As part of the process, teams researched existing quality standards such as ISO and the *Defect Evaluation List for Containers Made of Tubular Glass* by Harl, Horst and Polan. In addition, quality information was gathered from glass suppliers and pharmaceutical companies, as well as photos or drawings that could be used for illustrations of each defect that was being reviewed. Once all this information was gathered, the teams began to methodically analyze all the data with the intention of creating a list of the most commonly found glass attributes. Each and every defect was individually examined and challenged to make sure that the information included in the slide was within the scope and was consistent with the format that was originally created with the publication of TR-43. The information that is presented for each nonconformity such as the name, location, classification, definition, photo or drawing all represent a consensus of the Task Force (see **Figure 1**). However, note that the photos of the nonconformities are only illustrations, they do not represent or suggest limits.

One of the last steps of the process required that the proposed lexicons be sent out to independent reviewers for comments. The independent reviewers have since provided comments relative to the information and material that each one contained in the draft documents. This was a very important step in validating the lexicons and the work that was done. It allowed the team to receive constructive and/or positive comments from individuals who were not a part of the process. The team is currently in the final stages of completing revisions to TR-43 based on the comments and suggestions that were received.

It should be noted that the molded glass bottles and tubular glass vials lexicons have not been updated during this process and will be addressed at a later date. This revision strictly involves the addition of three more lexicons bringing the total to five. Once this revision to TR-43 is finalized and approved for publication, this technical report will represent a consensus document that is a compilation of the most commonly found visual

Figure 1



These are examples of photos that can be found in the revised technical report

glass attributes for molded glass bottles and tubular glass containers (ampoules, cartridges, syringes and vials). It is the Glass Task Force's hope that this report will serve the industry as an important element to existing documents in the evaluation and classification of nonconforming molded glass bottles and tubular glass containers.

TR on GMPs for Clinical Drugs

Joachim Leube, Bayer HealthCare

New options of therapy are needed for a considerable number of diseases. Nowadays research in this field has extended from classical big pharmaceutical industries to a large number of smaller, often just recently founded organizations. These firms have a huge innovation potential, but they also have a need for clear guidance of how to move a compound from the research laboratory to approval for commercial use. This need is enhanced by the recent changes in the regulatory environment, one example being the U.S. FDA guidance on *GMPs for phase I, Investigational Drugs*, which actually has been found confusing by a large number of experts in the field.

PDA is currently in an advanced stage of developing a technical report (TR) on, *GMP Points to Consider for Investigational Drug Products*. This report will cover the whole spectrum of clinical development from phase I through phase III, encompassing both chemical and biological therapeutic agents administered as finished drug products. Looking from a different angle, it covers all aspects from starting materials and production through testing; batch certification; release up to and including distribution; and the associated logistics of getting a safe and hopefully effective, finished product to the patient participating in the clinical trial. The report adopts an incremental approach to application of the GMPs in manufacture of investigational drug product while advocating an appropriate quality system at all phases of human clinical studies.

The TR starts by introducing the reader to the regulatory environment, highlighting the differences in regulations and expectations in the different regions.

Everyone participating in a clinical trial has the right of maximum protection against avoidable risks, including those arising from lack of quality of the investigational drug. The TR shows what to consider when setting up a state-of-the-art quality management system and how this can help in achieving the ultimate aim of product quality. The main elements of such a quality management system are highlighted, including systems for the management of documentation, changes, deviations, training and audits, among others. Included is also a differentiation or an incremental approach to the system as the investigational drug product moves from manufacture of early phase (I/II) to late phase (IIb/III) trials.

This approach is continued in subsequent chapters, which address specific areas of GMPs, consider where a simplified model might be still adequate for early phases and subsequently enhanced as necessary as production and controls move to later phase manufacture and knowledge of process and product increase.

In the area of materials management, the reader will find information on control over the supply chain, supplier qualification and other relevant topics to assure that the components and raw materials used for the investigational drug product are of the appropriate quality from arrival through their use in production up to and including the assigned expiry, retest or use by date of the finished investigational drug product.

The manufacture of investigational drug product is often challenging because of the limited knowledge of the toxicity, potency, and/or sensitizing potential of the active substance. The TR includes points to consider in the design and qualification of facilities, equipment and production processes used in the manufacture of investigational drug product, considering the important aspects of avoiding cross contamination or mix-ups, containment, cleanability and change over procedures between campaigns, while maintaining the necessary flexibility in the process and nevertheless ensuring that the manufacturing process is in a state of control. Not only are parenteral drug products covered, but the specific requirements for different types of dosage forms are also considered.

A chapter has also been written on quality control and laboratories that addresses topics such as sampling, method development, qualification and validation, as well as specification setting, expiry dating and stability testing requirements.

Packaging and labeling are particularly critical for investigational drug products due to the need for randomization and blinding for certain studies. The large variety of set-ups possible to flexibly adapt the packaging and labeling to the different clinical studies has been considered in this chapter.

Investigational drug product manufacturing and controls are reviewed as part of the certification and subsequent release (or rejection) of each batch, and the TR describes the pre-requisites for performing these tasks, as well as the options for extending expiry dates where applicable.

Last but not least, the topic of distribution and how to assure adequate control over the investigational drug product through delivery to the clinical trial site is explained, including modern, electronic approaches to distribution control.

The TR concludes with a section on references to the current guidelines and rules governing the manufacture, quality control and certification and release and distribution of investigational drug products. This TR is planned for publication by the end of 2010 or the beginning of 2011.

The task force for this technical report will help start-ups navigate through the confusing regulations that the FDA has unveiled in its guidance on GMPs for phase 1 and is intended to be a reference for everyone navigating the field and looking for current best solutions. Look for the next PDA conference about Clinical Trial Material scheduled for early 2011 on our website to find out more.

PDA/FDA Meeting Preview, continued from page 9

- Concurrent IG sessions: 4:45 pm. – 6:15 p.m.
  - **Supply Chain Management**
  - **Combination Products/Inspection**
  - **Quality Risk Management**
  - **Visual Inspection; Vaccines**
  - **Pharmaceutical Water Systems**

Wednesday, September 15:

- Concurrent PCMO Sessions:
  - **PCMO PO1, Process Validation & Verification: A Lifecycle Approach:** 1:00 p.m. - 2:30 p.m.
  - **PCMO RO5, Quality Risk Management for Packaging & Labeling:** 1:00 p.m. - 5:00 p.m.
  - **PCMO RO6, Risk-Based Auditing:** 1:00 p.m. - 2:30 p.m.
- **PCMO Task Force Leader's meeting:** 3:00p.m. – 6:00 p.m.

Thursday, September 16:

- **Early Phase Clinical Trial Materials Task Force:** 8:00 a.m. – 5:00 p.m.
- **Single Uses Systems Task Force:** 8:00 a.m. – 5:00 p.m.
- **Blow-Fill-Seal Task Force:** 9:00 a.m. – 5:00 p.m.

Learn more about *2010 PDA/FDA Joint Regulatory Meeting* at www.pda.org/pdafda2010

Journal Preview, continued from page 9

Research

Feroz Jameel, Chakradhar Padala, Nitin Rathore, Kapil Gupta, Ananth Sethuraman, "Impact of Uncontrolled vs Controlled Rate Freeze-Thaw Technologies on Process Performance and Product Quality"

Barry Fairand, Niki Fidopiastis, "Radiation Sterilization of Aseptically Manufactured Products"

Rajendra Redkar, Elizabeth Varmette, Brianne Strony, Daniel Haines, "An Assay for Measurement of Protein Adsorption to Glass Vials"

Emir Denkbas, Eylem Güven, Esref Oguz Güven, Cem Bayram, Osman Nuri Kazak, "Preparation and Characterization of Papaverine-Loaded Poly[(R)-3-Hydroxybutyrate] Membranes To Be Used in the Prevention of Vasospasm"

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Disinfection for HBV by Using A_0 Concept Defined in ISO 15883-Washer-Disinfectors"

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microorganisms may pose an equally serious threat to the patient or on product stability that may impact on the efficacy of the drug."

Dr. Guilfoyle presented some of the criteria he felt should be included when evaluating risks to the patient and product. He further stated that these criteria had been successfully used in court cases related to product contamination. The criteria presented include the following:

- **The microorganism(s)**

  When looking at the microorganism, it is important to ensure that you have the contaminated microorganisms isolated and purified. When doing this it is important to remember that mixed cultures can interfere with proper identification. One must also look for slow growing microorganisms like fungi (i.e., streak 14th day sterility tubes to look for possible contamination). If there are microorganisms of interest (suspect) keep the suspect microbial isolates on agar slants within sterile screw cap test tubes for subsequent epidemiology studies or DNA fingerprinting.

  It is also important to correctly identify the microorganisms found. This requires that appropriate tests be conducted, and that accurate identification is achieved. The accuracy of identification can vary depending on the instrument used and the source of the data base serving that instrument for final identification. For this reason caution should be taken to reduce the risks of instrument variability. One should clearly understand the limitations of the identification system they are using. For example, test cards and reagents should be properly stored. If a system requires a specific level of turbidity, it should be tested to ensure that the correct level of growth is achieved. One should also take care to use cultures that are of the correct age for the system being used. For some instruments, there may also be variability by carrying too much growth medium into the test suspension.

  It is also important to understand that the same organism can be identified as different species and/or different genuses when processed on some equipment.

  Another concern is the changing of microorganism names by organizations such as Bergey's. When the name is changed, one must be aware of all the different names that the organism had in order to ensure that subsequent contamination is or is not the same as previously identified. For example organisms previously known as *Pseudomonas* could now be identified as *Ralstonia pickettii*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Nitrosomonas*, or *Comamonas*.

  Once the microorganism is identified, it is also important to determine its characteristics. There are several ways to do this, including conducting a thorough literature search. It is useful to use multiple databases in this process. Additionally, the search can be in related fields like food, cosmetics, and so forth.

  The metabolic profile of the microorganism is another important characteristic. It can be assessed by determining the substances used by the contaminant for growth (e.g., in *Bergey's Manual*) and studying reaction results from phenotypic identification systems. This information can be compared to data on the product formulation to determine whether the product can enhance or promote growth of the contaminant.

  One should identify any unique tolerances to environmental conditions as this may impact the ability of the organism to grow or die off. Some examples of these types of conditions include: tolerance to high or low pH, tolerance to high salt concentration or high sugar concentration, low water activity, heat tolerances, and so forth.

  The ability to be resistant to antibiotics can also be important. For example, will the microorganism transfer antibiotic resistance to another more virulent pathogen in the product. This can impact the ability to treat patients, if they had an infection.

  One should also consider the natural habitat of the microorganism. For example, does it like water, air, botanicals, or soil environments? Along those same lines, consider whether the organism is associated with specific animals, plants, insects, or specific areas of the human body. Among common areas of the body with specific organisms are those associated with the fecal area, skin, throat, hair and so forth. Some of this type of information can be ascertained from the microbial identification and use of reference texts like *Bergey's Manual*.

- **The product characteristics**

  In addition to learning about the microorganism's characteristics one must also study the associated product characteristics. A good place to start is to look at the risk factors associated with the product. Consider the form of the product dosage. Is it a gel capsule, dry tablet, aqueous oral dosage form, an inhalation product, a topical or cream? There is a tendency to think that all products with low water activity values (A_w) ensure that microorganisms are not present. In reality the low water activity level may control the proliferation of microorganisms in the product but it does not indicate that there is an absence of potentially high bioburden already present.

  There are also risks associated with the methods used to sanitize product containers. Containers have the potential to be contaminated and transfer that contamination to the product.

  The product formulation can have an impact on the potential for microbial growth. It is important to understand and identify all of the ingredients used both for the active and excipients. The concentration of each ingredient also is important. The pH range of the product can be important in determining whether microorganisms will proliferate. One should not assume that the pH range stated is what is present in the product. It is useful to confirm

the pH values in your own laboratory. If the product uses a preservative system, the preservatives and concentrations should be identified.

As part of the product investigation a thorough review should be conducted of the manufacturing process. The production records should be assessed for unusual problems. Some examples might be extended hold or storage times or temperatures, or an intermediate step that was not performed correctly. Any water used in the production process should also be reviewed, including the associated microbial content. If contamination is present, it should be investigated for potential impact on the product.

The route of administration should also be considered, e.g., oral dosage form, topical application, nasal spray, or drops. Some organisms are a greater concern depending upon how they are introduced to the body.

One should also identify the underlying disease associated with the patient who is receiving the product. This is important as some microorganisms are a bigger threat to patients with specific diseases.

During this process one should also look at regulatory records such as customer complaints, product recalls, and GMP compliance for the product. One of the concerns is whether there is a common side-effect of the product that could mask the symptoms of the microorganisms in the product. The reason for looking at GMP violations is to assess whether one can indicate a potential source of the contamination from the violation.

The environmental monitoring data should also be reviewed to determine if the product contaminants have also been found in the data obtained. It is also important to assess whether the methods used would detect the organism if it was present.

- **The potential impact on patients**

The other important criterion that must be assessed is the potential impact of the contamination on the patients using the medication. Dr. Guilfoyle provides some specific factors that should be considered as part of this process of determining potential patient impact. Opportunistic pathogens will cause disease when they are subjected to the right conditions. As such, it is important to understand whether the target patients for the medication will provide the "right conditions" for the organism to proliferate.

Microorganisms that cause spoilage of food should be investigated as they may also degrade aqueous drug products. Contamination with molds can cause other risks due to their ability to cause allergic reactions. Molds can also cause difficult to treat infections.

Other considerations include whether antibiotic resistance to specific pathogens can be transferred via plasmids; whether high acid products can be selective for proliferation of acid tolerant pathogens (able to survive in the gastrointestinal tract) and whether high levels of microbial growth will adversely impact the active ingredient's efficacy.

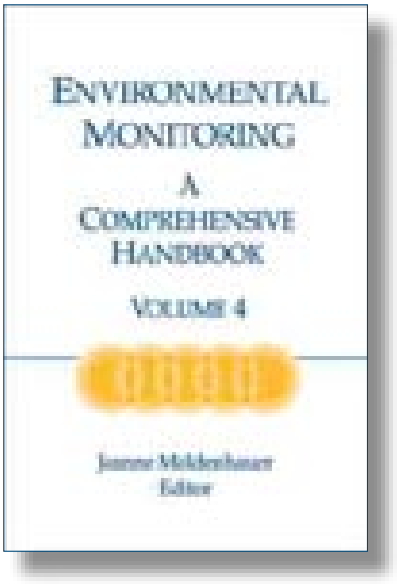
Dr. Leonard Mestrandrea, representing the USP's Microbiology and Sterility Assurance Expert Committee provided information on a proposed monograph for environmental monitoring and control of non-sterile drug product manufacturing areas. The intent of this proposed chapter is to use a risk-based approach for environmental monitoring. The intent of this approach is to understand the process, be able to define those areas with a potential for contamination to occur, and to establish appropriate procedures to monitor and control the process.

In this presentation several points to consider when performing the risk assessment were identified. These considerations included:

- The route of administration of the drug product
- The synthesis, isolation, and purification of the drug substance
- The microbiological attributes of the drug product excipients
- The formulation, chemical and physical attributes of the drug product
- The manufacturing process
- The dosage regime
- the age and medical status of the intended recipients of the drug product
- The administration of immunosuppressive agents and/or corticosteroids
- The presence of disease, wounds, organism damage and invasive medical devices associated with the recipient.

The considerations for risk assessment are quite comprehensive. The inherent problem associated with performing these risk assessments is that a large population of patients today has chronic diseases, may be immunosuppressed and is taking other medications. This can make the risk evaluations difficult to conduct, especially when it is virtually impossible to know all of the associated risks with all of the other potential medications to be taken.

There are also a large number of individuals undergoing treatment for cancer, where they may have one or more implantable devices, e.g., medication administration ports. Other patients have pacemakers, and other devices implanted. As such, trying to identify all of the associated risks can be quite difficult. In many cases a company's medical department may need to be consulted to aid in the assessment.



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Recent Sci-Tech Discussions: In-Process Bulk Sterility Testing

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.

Questioner: Hello,

Could anyone help me with regulatory references (guidances or regulations) related to in-process bulk sterility testing? Is it a formal requirement to do in process bulk or simply a requirement for vialed product for release?

Any references would be greatly appreciated. To clarify, I'm looking for requirements related to the fill/finish process for parenteral drug products.

Thank you in advance!

Respondent 1: Hello, The Aseptic Guidance from 2004 has a section related to time limitations (VIII). This is the section we have always targeted when conducting hold studies. The best part is the header of the page states "Contains Nonbinding Recommendations" which really gets to the point of this discussion! Good luck.

Respondent 2: For biologics it is more common to do in-process bioburden rather than sterility. The regulatory expectation is that by keeping the bioburden low there is less likelihood of microbial degradation of the biologic.

Respondent 3: [Questioner]: It is an EU requirement, GMP Rules, Volume 4, Annex 1 Section 80, to carry out a bioburden test on the bulk solution before sterilization. There should be limits for the allowed bioburden. This is not a sterility test.

It is also a requirement that the interval between solution prep and sterilization should be kept to a minimum. Many companies take a risk and fill and sterilize the product without waiting for the bioburden result. The risk is very small for a well-qualified facility and process using highly trained operators.

Respondent 4: Dear [Questioner], In-process bioburden testing is required, which is distinct from sterility testing, but in a way it is the same thing. In-process bulk bioburden testing is called for in FDA's 21 CFR Part 211.110(a)(6). If you are also shipping to the EU, the EU GMP Annex 1 also requires it. If you are also shipping to Canada, regulation C.02.029, Interpretation 77, also calls for it.

Bioburden testing may be done periodically when overkill terminal sterilization is used without parametric release, if that is your situation.

Respondent 5: While the Aseptic Guidance says "NonBinding" please remember that it also says "Pharmaceutical cGMPS."

Respondent 6: To my understanding, there is no regulatory reference to perform sterility on in process bulk, but it specifies to do Bioburden Testing on the same.

Respondent 7: An internet search for: "in-process sterility test of harvests" should give you the interpretation of the regs from several micro test vendors, such as unprocessed bulk testing (for protein and virus products). Within the biotherapeutics industry "unprocessed bulk" has many other descriptions, including cell/viral harvest, clarified cell/viral harvest, end of production cells or cells at the limit of in vitro cell age. Although the pharmacopeias and 21 CFR 610.12 do not reference or provide sterility guidelines for these sample types, the U.S. FDA documents *Points to Consider in the Characterization of Cell lines Used to Produce Biologicals* (1993) and *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (1997) do reference the need for sterility or bioburden testing on each unprocessed bulk lot. These two documents reference the 21 CFR 610.12 for guidelines on the appropriate sterility test methods to use. Since there is no reference in the pharmacopeias or 21 CFR 610.12 specifically related to unprocessed bulk material, no sampling guidelines are available either. However, industry practice is to use the sampling guidelines stated for bulk drug substance as detailed in the 21 CFR 610.12. Thus 10 mL/media (for a total of 20 mL) is recommended for sterility testing of unprocessed bulk material.

This rather long statement aligns with: *Points to Consider in the Characterization of Cell lines Used to Produce Biologicals:* "Testing for bacterial and fungal sterility is generally performed on the unprocessed bulk lot, the final bulk lot and the final product…." This includes section V. Quality Control Testing: A. Tests for the Presence of Bacteria and Fungi, which says "for required test procedures, see 21 CFR 610.12."

FDA's Draft Guidance for Industry: *Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases*, September 2006, Section III.E.5 Post-Filtered Harvest or Final Bulk says: "The post-filtered harvest or final bulk should be tested for bacterial and fungal sterility."

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Neeraj Agrawal, M. J. N. Chandrasekar, U. V. S. Sara, A. Rohini, "Synthesis, Characterization, and In Vitro Drug Release Study of Methacrylate Diclofenac Conjugate as Macromolecular Prodrug"

Technology Application

Ron Smith, Mark Von Tress, Cheyenne Tubb, Erwin Vanhaecke, "Evaluation of the ScanRDI® as a Rapid Alternative to the Pharmacopoeial Sterility Test Method: Comparison of the Limits of Detection"

Mohammed Ali, "A Novel Method of Characterizing Medicinal Drug Aerosols Generated from Pulmonary Drug Delivery Devices"

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Top Ten Myths of Container Closure Integrity Testing

Dana Morton Guazzo, PhD, RxPax

Three decades ago, testing a container closure system for integrity meant performing a product sterility test. As recently as ten years ago, container closure integrity testing (CCIT) meant microbial challenge tests, or in more progressive circles, dye ingress tests. Advances in package leak testing technology and shared research studies present a new opportunity to redefine CCIT. The following is intended to dispel some of the more popular CCIT misconceptions.

Myth 1: Dye ingress tests such as USP <381> Self Sealing Capacity are valid CCIT methods.

Compendial or International Standards Organization (ISO) dye ingress tests check the capacity of multi-dose stoppers to reclose upon repeated piercing with an injection needle **(1, 2)**. However, these tests are not validated, reliable or sensitive enough for whole package integrity verification **(3)**. Results are generally variable and subjective. Spectrophotometric dye detection does not eliminate risk of false positive or negative results. Another common dye ingress myth is that test method sensitivity is defined as the quantitative limit of dye detection. Rather, leak test method sensitivity is the demonstrated ability of the test to identify packages with specific defects among a random mix of no-leak and with-leak containers. A detection method able to identify minute traces of dye is useless if the ingress test's challenge conditions fail to draw dye into the package, or if the product itself blocks or clogs leak paths.

Myth 2: Microbial challenge tests are required to verify package integrity, and/or to validate the sensitivity of an alternate physicochemical CCIT method.

To many, validating a physicochemical leak test means performing a microbial challenge test comparison. However, no standard microbial challenge method exists to serve as a basis of such a comparison. Microbial challenge tests are notoriously probabilistic. Instead, leak test instrument performance qualification using appropriate traceable leak test standards is recommended. For example, vacuum decay leak test instrument performance can be verified by introducing an air leak into the test chamber via a NIST airflow meter. Post qualification, proper leak test method validation protocols require successful differentiation of multiple positive and negative control packages randomly tested over multiple days of operation **(4)**. In the same way, regulatory agencies previously expected microbial challenge data as part of a new product application for market approval. But today, successful U.S. regulatory agency market approvals may be supported solely with data from sensitive and appropriately validated non-microbial CCIT methods.

Myth 3: Valid CCIT methods must detect package leaks as small as 0.2µm in diameter.

The ideal leak detection method would identify all leaks from 0.2µm in diameter to large, visible defects in any product-package, rapidly, nondestructively and accurately. Such a method does not yet exist. If it did, the greatest challenge to proving its capability likely would be creating a submicron leak in a test package. Simulating submicron leaks with micro-tubes, etc has its own problems (see **Myth 4**). Laser-drilling technology reportedly can create defects as small as about 2- to 3-µm (nominal diameter) in laminate film, or about 4- to 5-µm in a glass vial. Holes smaller are readily blocked with debris and their sizes are not easily verified. Rarely, if ever, has a product recall occurred due to submicron-sized leaks. Instead, sporadic package defects or production processes trending out of control trigger more grossly leaking product missed by routine inspection. The most useful and practical leak test methods find small realistically viable leaks, but also those larger visible defects that are the source of many product-recall headaches.

Myth 4: Positive controls (with-leak packages) made by inserting needles, tubes, or pipettes into a package adequately prove CCIT method capability.

Inserting a wire, needle, tube or pipette into a parenteral glass vial, a syringe barrel or an elastomeric stopper is a less expensive and simple way to create a defect and may be useful for screening leak test methods. But, in many cases, long channels or wires artificially lodged into the package are no substitute for more realistic defects strategically positioned throughout the container, including at critical seal sites. Recent studies using laser-drilled holes in glass vial walls demonstrated that proteinaceous active substance in liquid product formulations may clog defects making it impossible to use leak test methods that rely on gas or liquid flow through the leak, such as vacuum decay or dye ingress **(5)**. This observation might have been missed if other types of artificial defects had been employed, and especially if solution other than the product itself had been used.

Myth 5: Helium mass spectrometry is the most useful method for package integrity validation.

Helium mass spectrometry is a highly sensitive leak detection tool for quantitatively measuring leakage from hermetically sealed packages. Historically, helium tests were used to better understand the probability of microbial ingress through known leak paths **(6)**. However, helium mass spec is only as accurate as the concentration of helium in the test package. Flooding a test package with helium tracer gas requires either puncturing the closed package, then resealing the injection site or flooding the package prior to closure. Both approaches are technique-dependent and are destructive to product-filled packages. Prior to leak testing, helium inside the test package can be quickly lost through a large leak, and a meaninglessly low leak rate may result. So while quite useful, helium mass spectrometry is not the method of choice for all parenteral package testing situations.

Myth 6: High voltage leak detection (HVLD) is a destructive leak test method.

Scientists from Hospira reported HVLD exposure caused ozone formation in the headspace of a small volume vial package

that lead to active substance oxidation **(7)**. Adequate nitrogen flushing eradicated this effect. Clearly, stability testing product exposed to HVLD is prudent. Still, continued successful utilization of HVLD for many types of pharmaceutical products supports this method's value.

Myth 7: Residual seal force (RSF) is a package integrity test method.

Residual seal force tests are an indication of the amount of force an elastomeric closure exerts onto the land seal surface of a vial **(8, 9)**. RSF tests are vital for verifying compression seal quality and consistency. However, RSF does not measure leakage. A package can have an ideal RSF and still have a crack in the glass. On the other hand, a low RSF does point to increased leakage risk at the vial/closure interface.

Myth 8: A patented leak test method is preferred.

A patented leak test instrument or technology is not necessarily reliable, robust, or sensitive. In fact, it may not work for a given product-package application at all. Before deciding on a leak testing approach or an instrument manufacturer, test, test and test some more. Leak detection predictions based on mathematical models or limited results using a handful of packages are no basis for a major capital purchase decision. Instead, test packaged product multiple times, multiple days, using randomly introduced no-leak and with-leak packages (both small to large defects). Compare various vendors' instruments using a common challenge-package set. Rent an instrument to allow a window of time for data generation before finalizing a purchase decision. Also, make successful instrument installation and validation a prerequisite for final payment to ensure satisfactory project completion.

Myth 9: Once a container closure system's integrity has been validated, there is no further need for CCIT.

A single product-package integrity validation study provides a point-in-time measurement that has little value in product-life-cycle quality assurance. It does not take into account day-to-day operational variations or package component lot-to-lot differences. Also, it provides no guarantee that product routinely manufactured and released for use is integral.

Myth 10:One leak test method works for all product-package systems.

Numerous leak testing approaches are useful, but none works for all applications. Package integrity technology has greatly improved in the last ten years, to the point that a toolbox of leak testing methods is essential for various product-package applications. Generally, vacuum decay methods are effective for testing powder-filled packages and non-proteinaceous liquid-filled packages **(10)**. High voltage leak detection works well for many package systems containing liquid formulations **(5)**. And frequency modulated spectroscopy with laser-based gas headspace detection is invaluable for packages requiring vacuum or inert gas headspace **(11)**. These nondestructive, rapid leak test methods are today's primary CCIT tools. Other methods will likely move to the forefront of leak detection as technology advances. But the days of relying solely on microbial challenge and dye ingress tests are long gone.

In conclusion, careful exploration of advertised CCIT developments and candid discussions within the pharmaceutical industry to share findings will ensure a meaningful and practical definition of container closure integrity testing–one that will drive improvements in future product-package system design, assembly and overall quality.

About The Author

Dana Guazzo is the President and founder of RxPax, LLC, a consulting firm committed to providing guidance to the pharmaceutical industry on primary package development. She has worked in the industry for about 28 years with such firms as the R.W. Johnson Pharmaceutical Research Institute, Schering Plough and the Warner Lambert Company.

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Industry Faces Challenges in Sterile Drug Manufacturing, Aseptic Processing

Walter Morris and Emily Hough, PDA

Pharmaceutical companies continue to have issues with GMP requirements for aseptic processing, and the U.S. FDA, under its policy of swift, aggressive and effective enforcement, is employing its full range of enforcement tools to improve compliance in this area.

For most of the 2000's, FDA's efforts included the issuance of regulatory guidances, public outreach and layered reviews of warning letters, in which the most serious infractions were cited and the most blatant violators were sanctioned. For manufacturers of sterile products, this approach resulted in a revised guidance on GMPs for products produced by aseptic processing and a focus on increased FDA education of the regulated industry through participation in industry workshops.

Nevertheless, the number of product recalls resulting from lack of sterility assurance has remained steady, and now it appears a number of firms are being cited for GMP violations that may have compromised the safety of their products. Teva Parenterals Medicines, Inc., Hospira, Inc. and the Genzyme Corporation are experiencing the most severe consequences for their alleged noncompliance. Extensive GMP problems, including issues with aseptic processing operations, resulted in a series of enforcement actions that included warning letters, recalled products, and, in Genzyme's case, a consent decree.

A number of the problem areas found at the three firms were addressed in the 2004 aseptic guidance, which was published with the intent of reducing the risk that these situations would develop. Other recent problems implicate inadequate Quality Systems, including the failure of the firms to trace contamination problems to the root causes.

A review of the problems encountered by these three companies should help other manufacturers of sterile drug products to avoid similar missteps.

Presence of Endotoxin Impacts Teva

Teva's regulatory issues originated with a July 2009 FDA inspection of the firm's Irvine, Calif., plant, where propofol is made. Agency investigators identified "significant violations" over the course of the inspection, including problems with endotoxin concentrations in the propofol product.

Specifically, the investigators noted in the FDA 483 that the QC unit failed to adequately investigate to the root cause "an 'out of trend' result for bacterial endotoxin from three vials" of propofol. Investigators took issue with QC's determination that there was no impact to the products and the unit's decision not to take any corrective actions based on test results. Moreover, QC's review of the batch record did not result in an identification of the source of the endotoxin contamination, prompting FDA to assert in the 483 that the source was still unknown. The investigators also took issue with the firm's assertion that "no corrective action can be implemented" since they had not identified the root cause.

This issue and the firm's response to the investigator's findings were addressed in

The Wrongs and the Shortages

FDA said that the aseptic guidance would "help reduce the incidence of manufacturing problems with this class of pharmaceuticals, which are often a major cause of drug shortages." **(1)**

In mid-April of 2009, Teva recalled the anesthetic propofol after elevated levels of endotoxin were found. **(2)** In May 2010, the firm announced that it would stop making the general anesthetic altogether, because the product is "hard to manufacture and the company gets little or no profit from it."**(3)** Hospira had to lift several lots of the same product off the market due to manufacturing defects. Two Hospira recalls of propofol extending into 2010, **(4)** compounded by Teva's problems, forced FDA to allow into the United States a similar drug that was approved in other countries in order to avoid a severe shortage of the product. **(5)**

While Genzyme faces the stiffest FDA penalties, it continues to market several products implicated in a 2010 Consent Decree. FDA is allowing the firm to continue producing Thyrogen (thyrotropin alfa for injection), a medically necessary product, in spite of findings of "foreign particle contamination" in some vials of the lyophilized product **(6)**, as well as three other lyophilized injectable products that are also made in the company's Allston Landing, Mass. plant. In May, the Agency published a "Dear Healthcare Provider" letter for the users of Thyrogen, Fabrazyme, Aldurazyme, Cerezyme and Myozyme warning about the potential for contamination. **(6)** The company is maintaining a web page to keep patients informed of the availability of these products as it sorts out manufacturing problems. **(7)** Because of the seriousness of the GMP violations at the plant, the firm is in the process of moving three of its lyophilized products to its Waterford facility in Ireland.

an FDA warning letter to the firm dated Dec. 11, 2009. **[Editor's Note:** PDA was unable to obtain a copy of the company's response in time for publication.**]** According to the warning letter, the firm notified FDA in an August 10, 2009 response that it would "commit to an increased sampling plan and testing of in process bulk emulsion and finished product" and "change the finished product release specification for bacterial endotoxin." But, according to the warning letter, FDA was dissatisfied with this response, because the company "failed to include a scientific rationale for [the increased sampling size]."

Regarding the firm's plan to change the release spec for endotoxin by reducing the acceptable level, FDA registered the following complaint in the warning letter: "Reducing the release specification for endotoxin levels may not alone mitigate the potential for adverse reactions for end users of the drug. It is a CGMP requirement that you implement adequate manufacturing practices and controls to prevent bacterial endotoxin contamination."

The Agency highlighted two Teva "operational investigation reports," November 2008 and January 2009, that reported incidences of vials used for filling propofol which were found to contain water as they were exiting the depyrogenation tunnel. This deviation was discovered in the vials prior to their entering the filling machine. Teva allegedly had already failed to investigate other propofol products which are manufactured on the same filling line.

FDA informed Teva that the firm did not describe "specific procedures for ensuring investigations are extended to other batches of the same drug product, or other potentially affected drug products, when unexplained discrepancies occur." FDA determined that the company's response also lacked details on how the investigations would be documented nor did it address current lots in distribution that may have been impacted by the deviation. Notably, FDA said, "You have not demonstrated that the water deviation was not present prior to November 2008, and particularly before you increased the number of visual examinations of vials following detection of the deviation."

> FDA is serious about its 2009 pronouncements that it will increase scrutiny of firms, if the numbers are any indication. In 2009, warning letters rose 6.5% from the previous year **(8)**, and the number of drug recalls exceeded the annual average from the previous 20 years. **(9)**

FDA admonished the firm for not conducting "adequate investigations"

The 483 and the warning letter include a number of other citations specific to aseptic processing, some of which are outlined in the box on pp. 25-28.

Teva, around the same time, had also been undergoing similar problems with its sister unit–Teva Animal Health. In August 2009, FDA announced that it filed a consent decree of permanent injunction against Teva Animal Health from manufacturing and distributing adulterated drugs, in response to ongoing compliance problems dating back to 2007. Its Ketamine Hydrochloride Injection (an animal anesthetic), was voluntarily recalled in December 2009 by the unit, after FDA cited it for having an "increased trend in serious adverse events associated with the product."**(10)**

Hospira's Challenges with Particulates

Hospira recalled three sterile products, propofol, liposyn and cleviprex emulsions, through a series of notices between November 2009 and May 2010 following the discovery of particulate matter contamination. The company's North Carolina plants in Clayton and Rocky Mount were inspected shortly after the November recalls; FDA issued a warning letter in April 2010.

At the Clayton facility, FDA ascertained that Hospira did not "assure adequate process design and control" for the three sterile products "to prevent objectionable particulate contamination (primarily stainless steel)." **(11)** The Agency noted that such controls would include: component controls, equipment suitability and maintenance and filtration. FDA cited Hospira for a contamination problem that has been "a persistent and serious issue…for multiple years."

A written response by Hospira promising that it would enhance monitoring programs for particulates and complete revalidation activities for all products manufactured at the Clayton facility was deemed "inadequate," as it was "unclear" to the regulators if Hospira had determined a root cause for the problem and an interim plan to ensure quality of products that were manufactured prior to the completion of the corrective actions was not provided.

FDA admonished the firm for not conducting "adequate investigations to prevent the recurrence of the problems and evaluate other potentially affected lots." FDA said that after the plant experienced particulate issues in January 2010 that led to product recalls, Hospira had failed to:

1. "Conduct testing to identify the foreign particulates (which were primarily stainless steel) until February 4, 2010"
2. "Place the remaining product from the two affected liposyn lots on distribution hold until February 5, 2010"
3. "Inspect remaining samples from associated lots until February 10, 2010." **(11)**

Hospira sent the FDA a new and revised procedure for dealing with investigations and initiating corrective and preventive actions; however the Agency felt that the company did not address the Clayton site's failure to follow the firm's exception report. It also did not explain why the samples were not inspected for three months to "verify adequacy."

FDA also noted a number of observations found at the Rocky Mount plant, but these did not involve aseptic processes. Problems with the manufacture of a ➤

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medical device were also outlined. The end of the letter noted that the Agency had addressed a similar violation, "failure to identify actions needed to correct and prevent the recurrence of defective product," in the August 2009 warning letter to Hospira's Morgan Hill, Calif., facility. "It is apparent that Hospira's attempts to implement global corrective actions after past regulatory actions by the FDA have been inadequate." **(11)**

Genzyme Aseptic Processes Targeted

Viral contamination in a cell bank, followed by persistent Agency findings of GMP deficiencies in aseptic operations and faulty quality systems led to Genzyme's Consent Decree. The agreement includes the typical accoutrements of strict Agency oversight and stiff monetary penalties.

Genzyme's problems with aseptic processing at its Allston Landing, Mass., plant have been documented in two separate FDA 483s, issued just 13 months apart. The first inspection of the Allston Landing, Mass., plant occurred in September 2008, and the follow-up inspection took place in October 2009. The first generated a 6-page 483; the second, a 22-page 483. The first inspection involved one FDA investigator; the second, five, including Thomas Arista, who also visited Teva's troubled facility.

Investigator observations included:

- Using vial pans in the depyrogenation process after they were identified as the source of metal particle contamination
- Failing to calibrate the filling line speed, stopper bowl feed or volumeric control since installation in 1994
- Employment of inadequate visual inspection procedure for finished products
- Rejecting media fill samples without explanation
- Failing to qualify all aseptic fill operators during each media fill; the personnel qualification procedure required personnel to participate in each media fill
- Maintaining inadequate records to document adherence to a decontamination plan for a bioreactor contaminated with Vesivirus 2117
- Designing an aseptic filling room that does not prevent ingress of viables/nonviables because of various flaws
- Allowing operations in the ISO-5 clean room to continue despite smoke studies demonstrating that airflow is not unidirectional

The consent decree does not list each of these observations specifically, but they are covered generally in the section that specifies the areas that are to be be inspected by an "independent expert" (section 4.B, subsections 1-9).

Subsections 4.B.5 and 4.B.6 cover the quality systems violations identified in the 2009 FDA 483. Here, the court reiterates the standard QS requirement that the Allston Landing facility establish a comprehensive, written QA and QC program that:

- Operates in coordination with, and under appropriate over-

sight of Genzyme's corporate QA/QC management
- Monitors trends, conducts and documents audits and investigations, and follows written SOPs to handle complaints, returns and adverse events
- Participates in the administration of corrective actions
- Oversees change control
- Reevaluates SOPs periodically and ensures that the plants SOPs address all facets of CGMP

The expert is also supposed to evaluate Genzyme's management structure to make sure there are adequate management controls in place for the manufacture of drugs. In addition, the employee training and qualification activities must be evaluated, as well as its laboratory controls, including specifications, standards, sampling plans and test procedures.

Under the terms of the consent decree, Genzyme has retained the services of the Quantic Group, an independent consultancy which provides service for FDA consent decree management. Genzyme expects its remediation efforts to conclude after 2-3 years. Once the remediation plan is fully completed, FDA will require five years of oversight and annual reports submitted by the Quantic Group. **(12)** Currently, the consulting firm has experts at the Allston Landing site in addition to other Genzyme locations and is working with the company to address facility and process improvements. **(13)**

Aseptic Processing – A Science, Not Art

FDA recognized over a decade ago when it was formulating its risk-based inspection program that products manufactured by aseptic processes posed a greater risk to consumers. The 2004 Guidance was issued to help manufacturers comply with regulatory expectations meant to safeguard patients.

However, as implied in this article, that Guidance alone is not a panacea. Companies must be ever vigilant to make sure they stay on top of their operations, with the help of strong quality systems. By ensuring that procedures are sound and that personnel don't deviate from the SOPs, the potential for issues like the ones summarized here can be minimized.

References on page 28

2004 Aseptic Processing Guidance Covered Many Problem Areas

The warning letters and FDA 483s received by Genzyme, Teva and Hospira contain a number of investigator observations that are also addressed in the 2004 FDA guidance, *Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice*. Below, the *PDA Letter* staff has matched some of the observations with corresponding sections of the guidance. NOTE: The three firms were not found in violation of the guidance, as FDA guidances are not enforceable. However, the guidance was issued to help firms comply with corresponding sections of the CGMP regulations, which are the source of the observations noted on the FDA 483s and the warning letters.

Section in Guidance (with excerpt)	Investigator Observation
IV. Buildings and Facilities: *As provided for in the regulations, separate or defined areas of operation in an aseptic processing facility should be appropriately controlled to attain different degrees of air quality depending on the nature of the operation. Design of a given area involves satisfying microbiological and particle criteria as defined by the equipment, components, and products exposed, as well as the operational activities conducted in the area.*	[COMPANY] failed to assure adequate process design and control of liposyn, propofol and cleviprex emulsion products to prevent objectionable particulate contamination (primarily stainless steel). Such controls would include, but are not limited, to appropriate component controls, equipment suitability, equipment maintenance, and filtration
IV. Buildings and Facilities: *As provided for in the regulations, separate or defined areas of operation in an aseptic processing facility should be appropriately controlled to attain different degrees of air quality depending on the nature of the operation. Design of a given area involves satisfying microbiological and particle criteria as defined by the equipment, components, and products exposed, as well as the operational activities conducted in the area.*	There is an observation window, approximately… that is used to observe the aseptic filling operations. The window seals and the sections where the window stainless steel frame meets, as confirmed by the Director of Quality, Production Supervisor, and Validation Manager, are not sealed such that… verified leak around the window stainless steel molding. The Senior Director Facilities confirms that there is no record to document that the interior surfaces of the wall are sealed.
IV. Buildings and Facilities, A. Critical Area – Class 100 (ISO 5): *Proper design and control prevents turbulence and stagnant air in the critical area. Once relevant parameters are established, it is crucial that airflow patterns be evaluated for turbulence or eddy currents that can act as a channel or reservoir for air contaminants (e.g., from an adjoining lower classified area). In situ air pattern analysis should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions. The studies should be well documented with written conclusions, and include evaluation of the impact of aseptic manipulations (e.g., interventions) and equipment design. Videotape or other recording mechanisms have been found to be useful aides in assessing airflow initially as well as facilitating evaluation of subsequent equipment configuration changes.*	The Operational Qualification Protocol for the Airflow Pattern Testing in the Class 100 (ISO5) Filling Room located at the Allston Landing Facility provides that the objective of this protocol is to define the requirements and acceptance criteria for the performance of the Operational Qualification of the airflow pattern testing in a fill room at Allston Landing. This protocol is in response to corrective actions/ preventative action (CAPA). There is no record to document the airflow pattern evaluation performed by the Quality Control department to support that the established acceptance criteria was achieved. The "Guidelines for the Performance of Airflow Pattern Testing for Clean Rooms and Laminar Flow Hoods, "provides minimum guidelines for performing airflow pattern testing (used to assess unidirectional air

It is important to note that even successfully qualified systems can be compromised by poor operational, maintenance, or personnel practices.	flow conditions in aseptic processing areas, support CGMP operations at Genzyme's Allston Landing and Framingham facilities." The Senior Director of Quality Operations confirms that the airflow pattern testing and requirements established in the document are a "must." The January 2009...evaluation video does not completely and adequately demonstrate unidirectional air flow within the ISO-5 (Class 100) aseptic fill zones and within the various ISO-5 areas in FF-2-016 e.g., personnel entering and exiting out of the… personnel… the filled vials from the tray loader… from the stainless steel… In addition, there are multiple HEPA filters in the 150-5 (Class 100) area i.e., above the… equipment that provides a vertical flow of air and a HEPA filter that provides horizontal air flow beneath the… equipment and the location where the depyrogenated and siliconized stoppers are off loaded from the… into the… stopper transfer vessel. The April 2006… study documents the airflow beneath the… moving in an upward direction rather than in a downward and outward direction. No evaluation has been performed to determine cause or impact to the sterilized and depyrogenated stoppers of the upward movement of the HEPA filtered air. The Certification of HEPA Filters, Biological Safety Cabinets and Chemical Fume Hoods," establishes that "A Metrology representative will also witness.. Pattern Analysis/ Testing for critical Class 100 Bio Safety Cabinets and Laminar Flow Hoods/devices." However, the Metrology Manager confirmed there is no data (i.e.. pattern video) to support the… pattern analysis."
IV. Buildings and Facilities D. Air Filtration, 2. High-Efficiency Particulate Air (HEPA): *HEPA filter integrity should be maintained to ensure aseptic conditions.*	Firm has not performed or determined the root cause for a HEPA filter leak failure that occurred in the critical area where the filling and stopping process of the propofol drug product was performed within the barrier shield over or near the stoppering equipment
IV. Buildings and Facilities, E. Design: *Both personnel and material flow should be optimized to prevent unnecessary activities that could increase the potential for introducing contaminants to exposed product, container-closures, or the surrounding environment...The number of personnel in an aseptic processing room should be minimized.*	The design of the aseptic filling room does not prevent the ingress of objectionable microorganisms and non-viable particles. Due to the design of the aseptic fill room and the… filling equipment there are up to… production personnel that are needed for the aseptic filling operations, which promotes the ingress of objectionable microorganisms and non-viable particles within the 130-5 areas.
V. Personnel Training, Qualification & Monitoring, C. Monitoring Program: *Personnel can significantly affect the quality of the environment in which the sterile product is processed. A vigilant and responsive personnel monitoring program should be established.*	[COMPANY'S] standard procedure for surface sampling does not establish sampling procedures for personnel during the capping of propofol prior to steam sterilization
VII. Endotoxin Control: *Adequate cleaning, drying, and storage of equipment will control bioburden and prevent contribution of endotoxin load… Some clean-in-place procedures employ initial rinses with appropriate high purity water and/or a cleaning agent (e.g., acid, base, surfactant), followed by final rinses with heated WFI.*	Firm has not provided data to validate that a flush for… minutes or washing the sampling ports in the… washer can remove or reduce the presence of bacterial endotoxin though the firm has provided a number of microbiology investigative reports that use these specified corrective actions Firm has taken no corrective action to bacterial endotoxin found in three vials of finished product. The Quality Unit reviewed the product and corrective actions and determined that there was no impact to the products and that no corrective action needed to take place. No area was identified in the manufacturing process as contributing to the high endotoxin. Another finished product lot was revealed to have a high endotoxin concentration. The Quality Unit determined that since the root cause of the endotoxin was unknown, no corrective action can be implemented. There is no assurance that propofol injectable emulsion 1% 10 mg/ml and 1% 100 ml is free of bacterial endotoxin. Two separate lots failed bacterial endotoxin tests yet met pre-shipment and post-shipment release and… units were released for distribution

IX. Validation of Aseptic Processing and Sterilization, A. Process Simulations: *To ensure the sterility of products purporting to be sterile, sterilization, aseptic filling and closing operations must be adequately validated... An aseptic processing operation should be validated using a microbiological growth medium in place of the product.*	[COMPANY] has not performed media fills, and therefore its internal practices, since its original 1998 ANDA submission. The firm's policies on validating the aseptic fill and terminal sterilization processes for small volume parenteral products say that process simulation runs (media fill runs) are performed at a… minimum) to requalify the total aseptic manufacturing operations for the filling process to support the sterility assurance validation. The company has not submitted a post approval change or a change being… for the ANDA that addresses the cessation of aseptic media fills and/or provides the scientific rationale with respect to the cessation and impact of the "sterility assurance validation" for the finished product. The Quality Unit has not taken into consideration obtaining samples of the non-sterile bulk solution to determine the presence , and level of, bacterial endotoxin prior to the aseptic filling process.
IX. Validation of Aseptic Processing and Sterilization, A. Process Simulation, 5. Line Speed: *The media fill program should adequately address the range of line speeds employed during production.*	The aseptic filling of all drug products into vials at higher speeds on the… filling line has not been adequately qualified for its current use. The data reported in validation studies documents that above… per minute, the stoppers clog in the stoppering machine and performance of the machine is affected.
X. Laboratory Controls, A. Environmental Monitoring, 1. General Written Program: *The monitoring program should cover all production shifts and include air, floors, walls, and equipment surfaces, including the critical surfaces that come in contact with the product, container, and closures.*	100ml lots of propofol injectable emulsion finished product, referenced in consumer complaints, did not include sampling for the manufacturing capping area during its dates of manufacture
X. Laboratory Controls, A. Environmental Monitoring, 2. Establishing Levels and a Trending Program: *Microbiological monitoring levels should be established based on the relationship of the sampled location to the operation. The levels should be based on the need to maintain adequate microbiological control throughout the entire sterile manufacturing facility. One should also consider environmental monitoring data from historical databases, media fills, cleanroom qualification, and sanitization studies, in developing monitoring levels. Data from similar operations can also be helpful in setting action and alert levels, especially for a new operation. Environmental monitoring data will provide information on the quality of the manufacturing environment.*	The sampling size used by the QC laboratory to determine sub-visible particulates via microscopic methods in small volume emulsion parenteral products and the sampling size used for the five day retain sample inspection is not scientifically sound.
APPENDIX 1: ASEPTIC PROCESSING ISOLATORS, A. Maintenance,2. Glove Integrity: *A faulty glove or sleeve (gauntlet) assembly represents a route of contamination and a critical breach of isolator integrity. A preventative maintenance program should be established. The choice of durable glove materials, coupled with a well-justified replacement frequency, are key aspects of good manufacturing practice to be addressed. With every use, gloves should be visually evaluated for any macroscopic physical defect. Physical integrity tests should also be performed routinely. A breach in glove integrity can be of serious consequence. The monitoring and maintenance program should identify and eliminate any glove lacking integrity and minimize the possibility of placing a sterile product at risk.* *Due to the potential for microbial migration through microscopic holes in gloves and the lack of a highly sensitive glove integrity test, we recommend affording attention to the sanitary quality of the inner surface of the installed glove and to integrating the use of a second pair of thin gloves.*	The isolator gloves are checked for leaks and holes via a so-called…; however, there is no written procedure to describe the…

APPENDIX 1: ASEPTIC PROCESSING ISOLATORS, D. Decontamination, 2. Efficacy:

An appropriate, quantified Biological Indicator (BI) challenge should be placed on various materials and in many locations throughout the isolator, including difficult to reach areas. Cycles should be developed with an appropriate margin of extra kill to provide confidence in robustness of the decontamination processes. Normally, a four- to six-log reduction can be justified depending on the application. The specific BI spore titer used and the selection of BI placement sites should be justified.

The most recent vendor audits of the BI and CI manufacturers did not include assistance from the microbiology departments, which would provide a scientific evaluation of the vendor's microbiology methods of analysis in support of the BIs and CIs.

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Quality & Regulatory Snapshot

Hailey's Comments

Drug Registration in Korea

Hailey (HeeYoung) Park, PDA

As a follow up to my article in May, I would like to now focus on the drug registration process in Korea. Since I came to work at PDA, I have realized that there was not a lot of information on the Korean drug registration process compared to what is available about Japan and China's processes. So, as I have been involved in the registration process for both generic drugs and biopharmaceuticals in the Korean Food and Drug Administration (KFDA), I wanted to share what I know.

Changes in the Korean Pharmaceutical Industry

Two events have helped transform the Korean pharmaceutical market over last several decades. The first was the Uruguay Round Agreements, which opened the Korean pharmaceutical market to the world in the late 1980's. This triggered the Korean pharmaceutical industry to transform from a generic- and domestic-oriented business to an innovative and multinational one. The second event was an amendment to the Korean Pharmaceutical Affairs Act in 2000, which established for the first time in Korea a system of distribution based on physician prescriptions for certain classes of drugs. Prior to this amendment, hospitals and drug stores could sell all drugs without a prescription.

These changes within the industry have led to considerable transitions of the Pharmaceutical Affairs Act and its subsidiary regulations. As the number of clinical trials have increased in Korea, the regulations to manage them have been revised to harmonize with international guidelines, including the introduction of the Common Technical Document (CTD) last year. The CTD should provide regulatory relief for new drug developers who are looking for overseas markets, as well as bring new therapeutics for unmet medical needs into Korea.

The Drug Registration Pathways

The Korean Pharmaceutical Affairs Act stipulates that every drug has to be registered to KFDA prior to being placed on the Korean market. There are two registration pathways: **Drug Approval** and **Drug Reporting**. The Drug Approval and Drug Reporting application can be compared to the U.S. FDA's NDA and ANDA applications. The primary distinction between the two pathways has to do with the known safety and efficacy of the product involved. If the product is known as safe and effective, it goes through the Drug Reporting process; if it is not known to be safe and effective, it goes through the Drug Approval process. New chemical entities, biologics, radiopharmaceuticals and narcotics are reviewed through the Drug Approval pathway, regardless of similarity to any products on the market.Each registration pathway requires different application data.

Prior to submitting a drug application, the applicant decides which registration pathway is appropriate for the product. The applicant can figure it out in the Act, or the applicant can discuss it with the KFDA. Figure 1 demonstrates the two pathways discussed below. Figure 2 is the organizational chart of the KFDA's drug review divisions.

The Drug Approval application, which is submitted to the KFDA Headquarters, is transferred to the Drug Approval and

2010 PDA/FDA Joint Regulatory Meeting *Preview*

RAQC, Quality and Regulatory IGs to Meet at PDA/FDA

At the *2010 PDA/FDA Joint Regulatory Meeting*, the Regulatory Affairs and Quality Committee (RAQC) will hold a strategy session and monthly meeting on Sunday, September 12 at 12:00 p.m. to 4:30p.m.

On Monday, September 13, two quality and regulatory interest groups, Quality Systems and Regulatory Affairs, will meet concurrently from 4:30 p.m. to 6 p.m.; and an invitation-only RAQC Regulatory reception will start at 6:00 p.m.

Learn more about the *2010 PDA/FDA Joint Regulatory Meeting* at www.pda.org/pdafda2010

Table 1: Examples of a Drug Approval and Drug Reporting Registration Pathway

Drug Approval	Drug Reporting
A drug has not shown to be safe and effective	A drug is deemed safe and effective
Examples	**Examples**
• New Chemical Entity (NCE) • Containing a modified active ingredient of different salts or isomers content from a previously marketed drug substance • Propose new indications • Change proportions of active ingredients • Change an administration route/dosage	• Generic drugs of marketed products • Over-the-counter drugs appointed in the Act (low potency vitamins, pain reliever, antacid, cough remedy, eye drops etc.)

Review Management Division (DARMD). This division looks through the application to see if it is acceptable and complete to file. If the application cannot meet the legal requirements or does not have sufficient data, this division issues a refusal letter or request letter for the insufficient data.

Filed data is sent to the other divisions to review the non-clinical, clinical and quality data according to the division's job responsibility. If the approval application needs a site inspection, the Pharmaceutical Quality Division will implement an inspection procedure. While the application is being examined, the division can require additional data to the applicant or a conference with the applicant.

After the review and inspection (when required), the responsible division sends all results to the DARMD to conclude if the application can be authorized. After their review, DARMD issues action letters announcing whether the application is approved, refused or approvable. If an application is deemed approvable, DARMD informs the applicant that more data and/or corrections are required. The application is then deferred until the satisfactory results are achieved.

The Drug Reporting application is submitted to the Medicinal Products Division, which has representatives in each of KFDA's Regional Offices. The Drug Reporting Application is sent to the district office containing the applicant's manufacturing site. It handles the application's filing, evaluates the legal requirements, performs a site inspection and issues the final decision about an application. The Center for Food and Drug in a Regional Office reviews the quality and equivalence data of the application. If an application needs further intensive evaluation, the Regional Office can cooperate with the other evaluation departments at the headquarters.

The Biopharmaceuticals and Herbal Medicine Bureau's Biologics Division reviews and approves vaccines, blood products and diagnostics for contagious diseases. The Advanced Therapy Products Division reviews and approves recombinant products, cell/gene therapeutics, and human tissue products. The Herbal Medicinal Division is in charge of modernized herbal medicine and traditional preparations which are contain herbal extracts. The Biopharmaceutical Policy Division manages biopharmaceutical policy and regulation revisions. It also implements preapproval inspections during application reviews.

The Application Documents

The Drug Approval Pathway application is used for all products eligible for this pathway, except new chemical entities (NCEs). NCEs now can be submitted using the Common Technical Document, which was adopted by the KFDA in March 2009. The CTD consists of five modules. Module 1 is about regulatory requirements; Module 2 is on an overview of data; quality data; non-clinical data; and clinical results make up module 3, 4 and 5 respectively.

The Drug Reporting application format is in the Act. The required data for drug reporting is mostly about chemistry, manufacturing and control (CMC) and equivalent to a marketed drug.

The KFDA Notification for a Drugs Registration, which is a subsidiary regulation of the Act, describes what kind of data shall be reviewed and how to write an application in detail for both the Drug Approval and Drug Reporting pathway. Below is a summary of CMC data requirements on the notification:

- Origin or discovery and pharmaceutical development
- Data on use in local or foreign countries
- Data on drug substances
  - Structural characterization
  - Physical and chemical characterization
  - Manufacturing process
  - Justification of specification and analytical procedures
  - Batch analysis
  - Reference standards and reagents
- Data on drug products
  - Components of drug product (including control of excipients)
  - Manufacturing process
  - Justification of specification and analytical procedures
  - Batch analysis
  - Reference standards and reagents

The Registration Time

The standard review process of a NCE application is 160 days, the longest review

time. When a GMP site inspection is needed, a NCE application can take up to 280 days to review. However, the time for a registration is dependant on data that is required under the Act. If a drug is an innovative drug for a life-threatening disease, KFDA initiates a fast-track review. A generic drug, without GMP inspection, can be registered within 100 days. The review time of a clinical protocol is typically 30 days. The review clock can be stopped when any action letter is issued or when the KFDA asks for supplemental information.

A Drug Manufacturer/Importer

In the past, only a company who had a manufacturing facility was able to hold a drug marketing license with its own name in Korea. It was not allowed for a small venture company who could not afford to establish a GMP facility to register its own named product using a contracted manufacturer. However, the Korean government amended the Act in order to boost a new drug development in 2008. Now, any party who has been developing in Korea can be a license holder without any facility by using a contract manufacturer.

A company who imports therapeutics into Korea has to have a facility to maintain the quality assurance of a drug. But the company can utilize a contract manufacturer for a quality control laboratory and product logistics although the responsibility for the quality is still on the importer, a license holder. Under the Act, this importer is a liable party and must maintain the quality of the imported, licensed drug in Korea. The overseas original manufacturer cannot directly be an applicant and/or a legal license holder. It has to have a representative partner or subsidiary offices. ➤

Figure 1: An overview of the drug registration processes

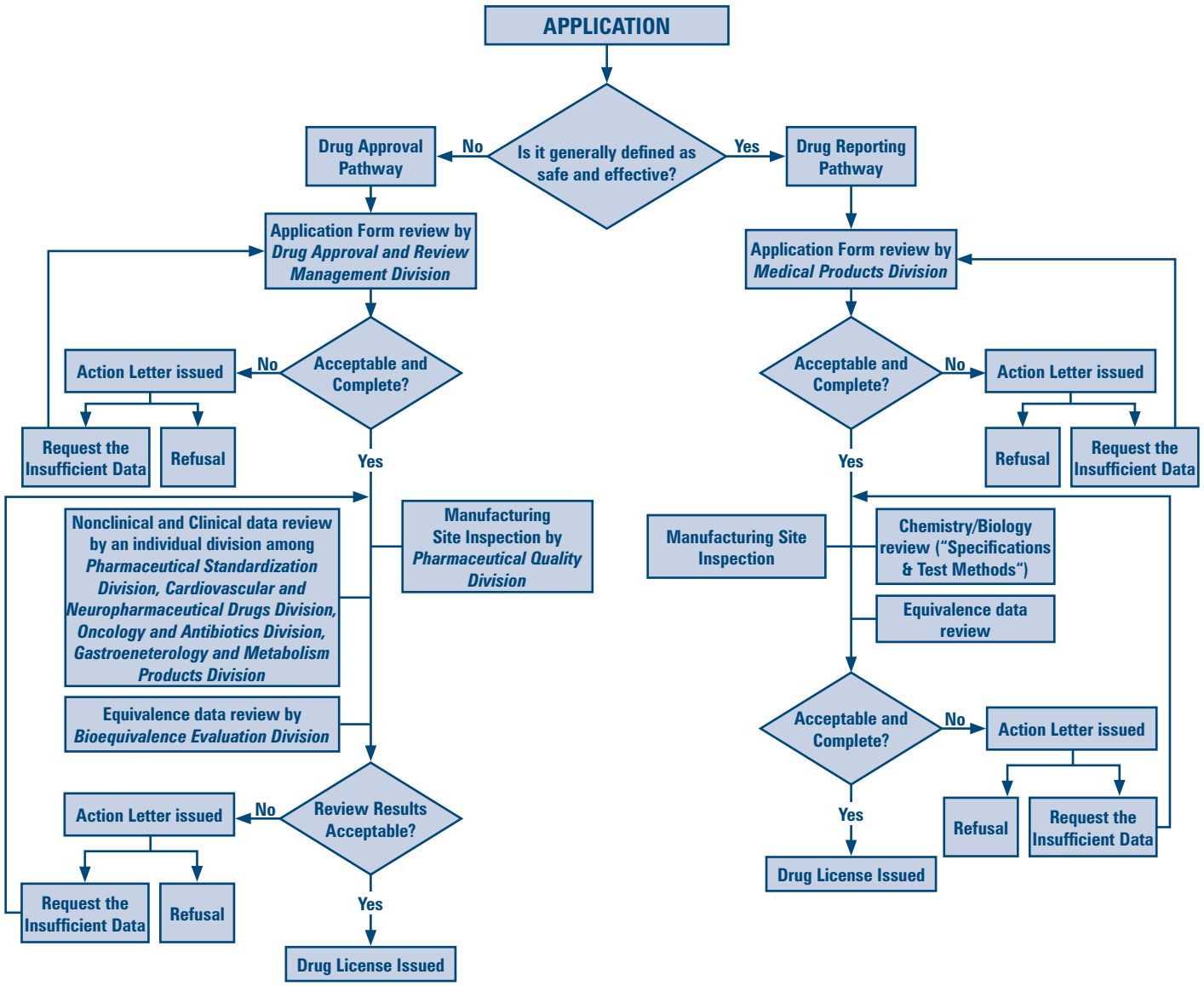

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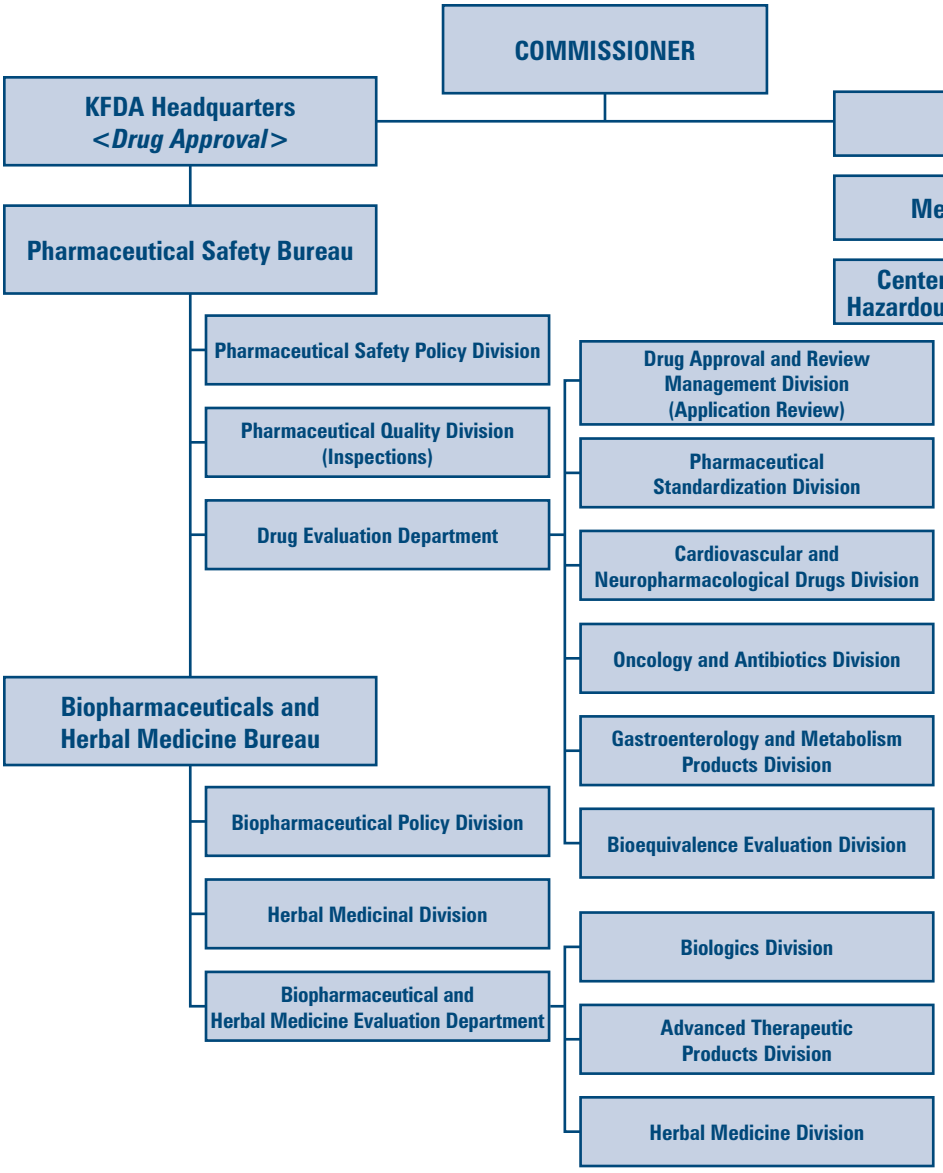
Figure 2: KFDA organizational and lines of responsibility as they pertain to drug registration



Understanding these recent considerable transformations of the pharmaceutical environment in Korea, it seems obvious that KFDA's policy about the drug registration system will keep moving toward international harmonization and provide motivation for new drug research, as KFDA is expected to adapt more components and ideas of international guidelines into the Korean regulations. It is also focusing on strengthening the drug application review process for novel therapeutics.

Stay tuned for my next article on GMP inspections in the September issue!

Design Specification – Missing Link to Knowledge Management

Carol DeSain, Tamarack Group

As the pharmaceutical industry establishes a risk-based life cycle approach to product development, manufacturing and marketing, it is instructive to compare their approach to other allied industries which have been doing this for years. The medical device and in vitro diagnostic industries (device industry), for example, implemented "design controls" for product development and a quality system approach for operations, codified in 21 CFR 820. In addition, the device industry has successfully implemented a risk-based, life cycle approach over the last 15 years and in their experience, knowledge management has not been a focus of attention. This is because the device industry has always had the tools of knowledge management: the *product design specification* and the *device master record*. This article will introduce the product design specification and provide an example of how it can be used to support knowledge management across the product life cycle in the pharmaceutical industry.

Translating *design control* requirements of a device product into a pharmaceutical approach is not a straight-forward exercise. Although the essential elements of the product development process are the same for all products, each sector of the medical product industry has evolved to a common approach (a risk-based and science-based quality system for the life cycle of the product) on a different timeline and with differing priorities. In this journey, both sectors have developed their own terminology (e.g., design control vs. quality-by-design) and they have developed

their own approach to the knowledge management of product development. If these differences could be easily understood and adapted as appropriate, then they could be used to test and strengthen each industry's approach to product development. The barrier to such a harmonized approach is often a simple misunderstanding of terminology, and the term *specification* represents one of those examples.

All Specifications Are Not the Same

The term specification in the pharmaceutical industry usually refers to release specifications for materials, components, intermediates and finished products. Release specification documents specify quality attributes, associated testing controls and acceptance criteria that the material or product must possess before it can be used in production and/or released for distribution; purchasing and material controls (storage conditions and expiration dating) are often also associated with these specifications. "Specification" for pharmaceutical products is defined in ICH Q6A, *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, as:

A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. Conformance to specifications means that the drug substance and/or drug product when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Testing to assure conformance with specifications is a routine and fundamental part of drug and biologic manufacturing. It is a regulatory requirement to test incoming raw materials for identity, and it is common practice to test or inspect all incoming components. Similarly, every finished product batch is tested for conformance to specifications before it is released to the market.

In contrast, the term specification does not have the same meaning or the same role in routine manufacturing in the device industry. For example:

- The term specification refers to a type of document, e.g., product design specifications, purchasing specifications, etc. In 21 CFR 820 it is defined as any *requirement with which a product, process, service, or other activity must conform.*
- The device industry does **not** routinely test incoming materials or finished products, as is common in the pharmaceutical industry; instead it relies on purchasing specifications for material control, routine, in-process inspection procedures for finished product control, and parametric release for assurance of sterilized products.

Knowledge Management: The Purpose of the Design Specification

Although both industry sectors develop products, gather information and share it with regulatory authorities to gain market ➤

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authorization, the documentation of this information/knowledge during product development and the use of this knowledge routinely after product approval remains significantly different between the device and pharmaceutical industries.

These differences have been created by different regulatory environments (product development in the device industry has been regulated by design controls for more than 15 years); and different business environments (time-to-market for new device products and improved device products is significantly shorter and use of contract manufacturing is more prevalent).

The product design specification in the device industry is the output of the product development process. It is a document or set of drawings that contain all of the product attributes to assure that the product will meet its intended use.

There is no document commonly created or used in the pharmaceutical industry that is equivalent to the design specification. The information gathered during the development of a device product and documented in a *product design specification* is similar to the type of information gathered during drug or biologic development; but, the knowledge from pharmaceutical development is documented in the regulatory submission instead of a controlled, internal document. The result is that the regulatory commitments for the device industry are available routinely to support the decision-making of change control, CAPA and on-going product development. The absence of this knowledge resource in the pharmaceutical industry has led to a disconnect between the product knowledge of the regulatory submission and the process knowledge of routine operations. It is no wonder that knowledge management has risen to the top of international, consensus standards like ICH Q10 for the pharmaceutical industry.

The Difference Between a Release Specification and a Design Specification

A release specification might contain, for example, a product attribute for sterility which would be associated with an acceptance criteria of "sterile" and a method for determining sterility, such as USP 71, *Sterility Testing: Membrane Method*. A *design specification* that also contained a product attribute for sterility, in contrast, would describe the relevant attributes of the product's sterility, e.g., it would indicate that "sterile" means that the product has a SAL (sterility assurance level) of 10^{-6} when sterilized by moist heat in compliance with ISO 11134 standards.

The *design specification* establishes the claim of sterility for the product. The *release specification* simply identifies how sterility will be confirmed routinely. The information about the sterility assurance level is a necessary claim for both the device and pharmaceutical product; the difference is in where that information is located. In the device industry, it is located in a product design specification document that can be provided in regulatory submissions, used routinely in change

Table 1: Sample Container Closure System Design Specs

CCS DESIGN SPECIFICATIONS FOR PRODUCT XYZ	
CCS ATTRIBUTE	**METHOD**
Vials/stoppers meet their design specifications	See tables 2 and 3 below
CCS is not significantly damaged by shipment. Product quality is acceptable.	Shipping tests designed by Product Development to include stability testing of product.
Product is not altered by interaction with CCS., e.g., acceptable turbidity, pH change, reducing agents, heavy metals, extractables,	USP <381>
Product is not altered by interaction with CCS., e.g., in vitro biological reactivity; agar diffusion	USP <87> and if required, USP <88>
Product shall meet requirements for small volume parenterals particulates	USP <788>
CCS seal shall not allow air to leak into product	Stability study according to ICH Q1A
CCS seal shall not allow loss of product or moisture over time	USP <1207>
CCS seal integrity shall keep product sterile over its shelf life	Stability study according to ICH Q1A Guidance for Industry – Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products
	Shelf life incubation of media fill vials Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice
	Dye penetration studies of CCS Guidance for Industry – Container Closure Systems for Packaging Human Drugs and Biologics

management decision-making and/or shared with contractors. In the pharmaceutical industry, this information resides in the regulatory submission, far away from routine operations.

In another example, a release specifications for a container-closure system (CCS) such as a glass vial and stopper includes component identification and testing of physical and dimensional attributes. The design specifications for the CCS includes safety, compatibility and manufacturability requirements for the vials and stoppers.

How to Start?

Developing a pharmaceutical product is the same as developing a device product; a product sponsor starts with a detailed understanding of what the finished product must be and do, i.e., intended use, safety and performance requirements. In the device industry this is called *design input* and the information is established in a document such as a *product requirements document.* **(1)** In the pharmaceutical industry the information should be established in a document such as a *quality target product profile*, as suggested in ICH Q8(R2). Both documents (design input/product requirements and quality target product profiles) form the basis-of-design for the product. Each approach to product development expects that market/user/regulatory requirements will be translated into measurable, technical, quality criteria for the proposed product.

When development is complete in the device industry, these technical requirements are used to establish design specifications. **(1)** At the conclusion of the product development process and during technology/design transfer, design specifications are formally transferred to commercial manufacturing operations where they are used routinely to inform contract manufacturing/testing relationships, CAPA investigations and change control decisions.

Design specifications, established in controlled documents that are available in the manufacturing environment, should serve to minimize the likelihood of design creep during routine commercial production. Currently in pharmaceutical operations, manufacturing does not usually know the commitments made in global regulatory submissions and corporate regulatory groups do not often know how changes might impact design. In addition, design specifications should support the triage of change control, e.g., changing a design specification is a significant change that should require regulatory oversight and likely pre-approval while changing a release specification is a change that should require only regulatory notification if the product continues to meet its design specification.

An example is provided in **Table 1** for a container-closure system design specification. **[Editor's Note:** See **Table 2** and **Table 3** for examples of Stopper Design and Vial Design Specifications.**]** This design specification would be accompanied by appropriate design drawings of the components. In the development of the pharma-

ceutical product, a container and closure should be selected and verified to meet these design specifications. Should the company decide to develop a new stopper, then the new stopper would be required to meet the same CCS design specifications.

Device Master Records - The Link to Product Knowledge

There are many design specifications created during product development in the device industry. These include design specifications for materials, components, manufacturing processes, testing processes, processing equipment, software, packaging, labeling, etc. These specifications are organized to assure that they are complete and retrievable in a Device Master Record (DMR), often formatted as a DMR index or database. This is a requirement of 21 CFR 820.181. *The DMR for each type of device shall include, or refer to the location of, the following information:*

Table 2: Sample Stopper Design Specs

STOPPER DESIGN SPECIFICATIONS FOR PRODUCT XYZ	
STOPPER ATTRIBUTE	**METHOD**
Elastomeric closures are 20 mm serum stoppers	See attached drawing. (Note: Drawings are supplied by vendors)
Complete chemical composition is known and confirmed for stopper components.	Purchasing specification Residue on ignition (ash) USP <281>
Elastomeric closures are sterile (SAL 10^{-6})	ISO 11137
Elastomeric closures are non-pyrogenic	Processing validated for 3 log reduction
Elastomeric closures can withstand steam sterilization.	Seal integrity testing of processed product components over shelf life.
Elastomeric materials are biocompatible	USP <88> USP <381>
Product shall be designed to minimize the use or concentration of silicone used in primary packaging materials.	Purchasing specification
Compressibility of elastomeric closures, dimensional tolerances of stopper and vial rim must assure adequate sealing.	Capping study designed in house Guidance for Industry – Container Closure Systems for Packaging Human Drugs and Biologics
Stoppers shall not contain silicone.	Purchasing control
Stoppers shall be available in sterilizable bags	

Table 3: Sample Vial Design Specs

VIAL DESIGN SPECIFICATIONS FOR PRODUCT XYZ	
VIAL ATTRIBUTE	**METHOD**
Vials are designed as 10 ml molded glass	See attached drawing. (Note: Drawings are supplied by vendors)
Vials are molded glass and meet USP Type I Glass Testing	USP <661> Chemical Resistance USP <221> Arsenic
Vial shall allow light to be transmitted onto product.	USP <661> for containers: light transmission
Volume in vial shall be sufficient for intended use	USP <1151>
Glass Vials are sterile – SAL of 10^{-6}	ISO 11137
Glass Vials are non-pyrogenic	Processing validated for 3 log reduction
Glass vials are biocompatible.	USP 661
Liquid, formulated product shall be in a container closure system that is sealed in a manner that prevents loss of contents or penetration of microbial contaminants or chemical or physical impurities when tested by liquid immersion.	Liquid immersion studies PDA TR 27 USP 1207
Vials shall have a coating other than silicone.	Purchasing control
Vials shall be provided in honeycombed, shrink-wrapped configurations.	

These examples cite methods acceptable in the United States

(a) Device specifications including appropriate drawings, composition, formulation, component specifications, and software specifications

(b) Production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications

(c) Quality assurance procedures and specifications including acceptance criteria and the quality assurance equipment to be used

(d) Packaging and labeling specifications, including methods and processes used

(e) Installation, maintenance, and servicing procedures and methods

An understanding of this regulation is facilitated by an understanding that the word "specification" in this context refers to design specifications. In addition to the design specifications, data, observations and information to verify that a given product meets its design specifications can be linked in such a database. This is one approach to knowledge management.

Product and Process Design Space

It is not difficult to see the role of the product design specification in establishing design space. Traditionally, the design space for a pharmaceutical product has been defined in the regulatory submission. When these commitments, derived from the output of product development, are also established in internal documents, such as design specifications, design space can have an active life in routine operations. In a manner that could be used for decision-making in investigations and change control.

Points to Consider

The pharmaceutical company of the 21st century has to communicate the details of its products and processes requirements to regulators, corporate partners, contractors and suppliers effectively, reliably and consistently, without compromising proprietary information. This is called knowledge management.

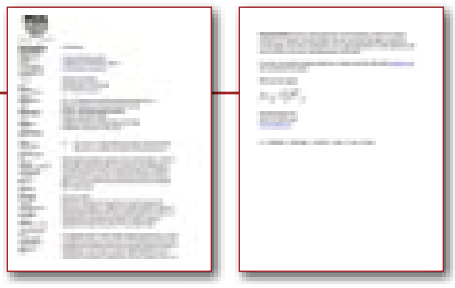
Product design specifications are the basis of knowledge management in the device industry, as it provides a reliable source of information about the output of product development, and are the basis of design for commercial operations. These design specification documents serve as the liaison between product and process, between assessors and inspectors, between product development and commercial manufacturing. As the pharmaceutical industry develops it's own way forward, the experiences from the device industry are points-to-consider along the way.

About The Author

Carol DeSain is the President and an Independent Consultant at the Tamarack Group. She has worked in the industry for more

continued on page 42

PDA Cautions Against Unclear Language in EU GMP



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

31 May 2010
European Medicines Agency
Compliance and Inspection, London
ADM-GMP@ema.europa.eu
European Commission
Pharmaceuticals Unit, Brussels
entr-gmp@ec.europa.eu

Reference: EU Guidelines to Good Manufacturing Practice, Part 1
Medicinal Products for Human and Veterinary Use
Chapter 1, Quality Management System
Brussels, 18 November 2009
ENTR/F2/MT/AM/jr D (2009) 37658, 18 Nov 2009
Deadline for comments: 31 May 2010

To: Responsible Person: European Medicines Agency, Inspections Sector
Responsible Person: European Commission, Pharmaceuticals Unit

PDA is pleased to provide comments on the revised Chapter 1 of the *EU GMP*, dated 18 November 2009. Our comments were prepared by an international group of volunteer experts with experience in GMP and regulatory affairs. They consist of one general comment, mentioned below, and a series specific technical comments found in the attached EMA matrix format.

General comment:
While PDA understands the importance of incorporating ICH Q10 principles into Chapter 1, we believe it should be done with a balance in understanding ICH Q8, Q9 and Q10 are optional guidances. As such, it is desirable their incorporation into Chapter 1 should not result in heightening the legal requirements for the European GMPs.

The language used for mandatory GMP standards should be clear, concise and objective. However, some revisions of the Chapter have the tone and language found in guidance documents, thus being subjective and open to interpretation. In such cases it is unclear if GMP expectations can be consistently interpreted and followed by users (for example, section 1.1.i).

Recommendation: We have made appropriate recommendations related to the above comment in our specific comments below. We also recommend the Agency review the revised chapter and remove wording that is not a legal expectation but rather guidance, and rely on ICH Q10 as the source detailed guidance information.

If you have any questions please contact me, or James Lyda of the PDA staff (lyda@pda.org) who coordinated this project.

With very best regards,
Georg Roessling, Ph.D.
Senior VP, PDA Europe

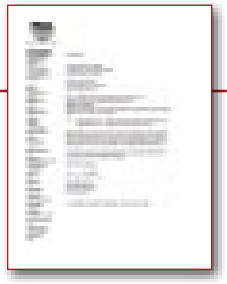
Design Specifications–Missing Link to Knowledge Management, continued from page 41

than 25 years, with start-ups, global corporations, contract manufacturers, and allied industries in the U.S. and Europe. Prior to consulting, Carol worked in basic research (biochemistry, enzymology, and genetics), product/process development and aseptic pharmaceutical manufacturing.

References

1. C.V. DeSain "Product Requirement Documents – Establishing Consensus about Product Design," *BioProcess International*, February, 2007, pp. 22-31.

PDA Recommends Specific ICH Wording In Chapter 2 of EU GMP



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Compliance and Inspection, London
ADM-GMP@ema.europa.eu
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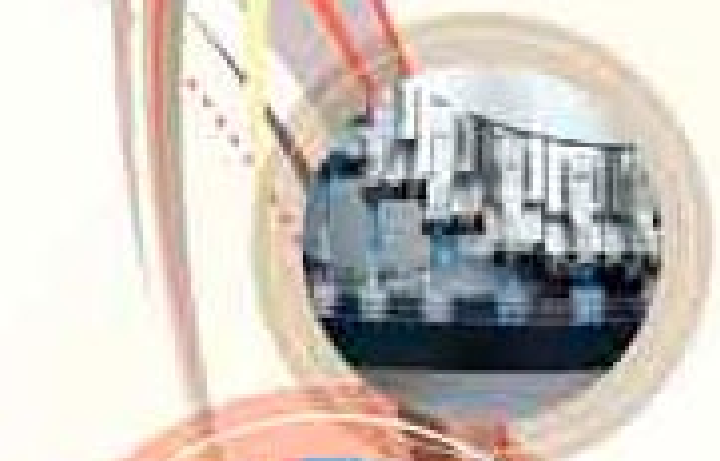
Pharmaceuticals Unit, Brussels
entr-gmp@ec.europa.eu

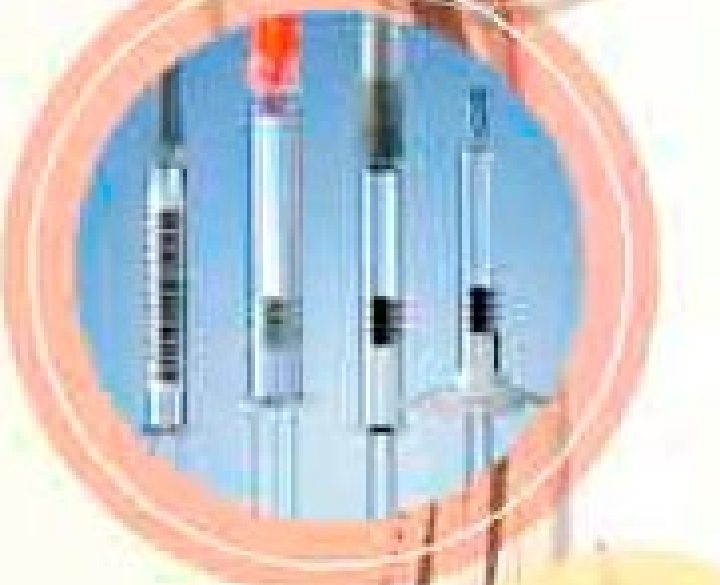
Reference: EU Guidelines to Good Manufacturing Practice, Part 1
Medicinal Products for Human and Veterinary Use
Chapter 2, Personnel
Brussels, 18 November 2009, ENTR/F2/MT/AM/jr D (2009) 37672, 18 Nov 2009
Deadline for comments: 31 May 2010

To: Responsible Person: European Medicines Agency, Inspections Sector
Responsible Person: European Commission, Pharm. Unit

PDA is pleased to provide comments on the revised Chapter 2 of the EU GMP, dated 18 November 2009. Our comments were prepared by an international group of volunteer experts with experience in GMP and regulatory affairs. Our three specific comments are presented in the attached EMA matrix format.

If you have any questions please contact me, or James Lyda of the PDA staff (lyda@pda.org) who coordinated this project.





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North America

Agency Data Standards Plan to Allow More Efficient Review of Standardized data

A draft document, entitled, *CDER Data Standards Plan Version 1.0*, is now available for public comment. The U.S. FDA draft plan outlines the general approach proposed for the development of a comprehensive data standards program in CDER by identifying objectives of the program; processes that will be developed, and a set of recommended projects to begin in 2010.

The standards plan will ensure the development and successful use of data standards for all key data needed to make regulatory decisions, since currently the lack of standardized data does not allow CDER to efficiently and effectively perform review processes of items such as data submissions.

Comments are due by September 15.

Agency's CDER, CBER Seeks Feedback on Product Labeling Indexing Process

The U.S. FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) are currently indexing certain categories of information in product labeling for use as terms to search repositories of approved prescription medical product structured product labeling. CDER and CBER have established a public docket to provide an opportunity for interested parties to share information, research and ideas on FDA's indexing process.

Previously, the Agency has identified the pharmacologic class as a top priority for indexing of product labeling information; FDA is now announcing that medical product indications is another category of product labeling information that is a high priority.

Public Workshop on Drug Resistance, Development in Held in July

A public workshop, sponsored by the National Institute of Allergy and Infectious Diseases and the Infectious Diseases Society of America will be held on July 26-27 in Silver Spring.

The workshop will address scientific and potential research issues in antibacterial drug resistance, rapid diagnostic device development for bacterial diseases and antibacterial drug development.

New BE Study Procedures Articulated in FDA Guidance

The U.S. FDA has released a guidance entitled, *Bioequivalence Recommendations for Specific Products*, which describes a new process for making available recommendations on how to design product-specific bioequivalence (BE) studies to support abbreviated new drug applications (ANDAs). Under this process, applicants planning to carry out such studies are able to access BE study guidance on the FDA website. The Agency believes that the use of the internet will streamline the guidance process and will provide a meaningful opportunity for the public to consider and comment on product specific BE study recommendations.

Agency Seeks Feedback on Methods for Co-Developing Investigational Drugs used in Combination

The U.S. FDA wants public input on how two or more novel, investigational drugs used in combination to treat a single disease or condition can be clinically evaluated. The Agency is establishing a docket to collect public comment and wants to use the information received to publish guidance for industry.

Comments should be submitted by September 7.

U.S. FDA Emergency Call Center Information Amended

The Agency has published a final rule amending their regulations to reflect changes in the contact information for the U.S. FDA's Emergency Call Center.

The affected sections of the regulations are 21 CFR Parts 106 (Infant Formula Quality Control Procedures); 107 (Infant Formula); 312 (IND's); and 803 (Medical Device Reporting).

The new contact numbers are 866-300-4374 (phone) and 301-847-8544 (fax). The change is effective June 11.

Key Regulatory Dates

Comments Due:

September 7
Comment on the Agency's Methods for Co-Developing Investigational Drugs used in Combination

September 15
An Agency draft document, entitled, *CDER Data Standards Plan Version 1.0*, is now available for comment

Updates:

The Agency has updated its Emergency Call Center Information

Workshops:

July 26-27
Public workshop, sponsored by the National Institute of Allergy and Infectious Diseases and the Infectious Diseases Society of America

Risks to Changing Sterile Drug Sites Discussed

Emily Hough, PDA

In late May, I was invited to go to PDA's Capital Chapter dinner meeting to hear **Cliff Campbell** speak about his project on changing sterile drug manufacturing sites that he worked on in conjunction with regulators from the U.S. FDA. I looked forward to going so I learn more about Cliff's assignment.

The project started in 2008, when FDA CDER's Office of Pharmaceutical Science (OPS) posted a solicitation directed at consultants regarding the completion of a 12-month research assignment on sterile drug manufacturing site location changes. The purpose of the assignment was to demonstrate that risks due to changing manufacturing site locations can be managed within the manufacturer's change control process, so that a supplement to an application is not required. The solicitation emphasized that manufacturing site location changes using change control processes had to be based on CGMPs and contained specific criteria to be fulfilled as part of the contract process. Cliff, CEO, Campbell Informatics, was chosen as the consultant to research and assess the risks of changing sterile drug manufacturing sites.

Cliff's presentation in Gaithersburg, Md., was based on a paper, entitled, *Assessing Risks of Changing Sterile Drug Manufacturing Sites*, which he co-authored in conjunction with **Stephen Langille**, PhD, Senior Microbiology Reviewer, OPS, CDER, U.S. FDA, in the *PDA Journal of Science and Technology* January/February 2010 issue.

Specifically, Cliff needed to deliver a risk analysis that proved that "sterile manufacturing processes, synthetic and biotech, can be described in such a way that demonstrates to a reviewer that the risk associated with changing the manufacturing site location can be managed within the manufacturer's change control process and as part of the CGMP."

He worked closely with CDER/OPS and prepared a work plan identifying the project scope, timelines and associated deliverables. Terminal sterilization was the agreed platform for synthetic drugs and aseptic processing was chosen for biotech drugs. Interviews were conducted using mainly Agency guidance documents and separate question sets were used for the synthetic and biotech phases of the assignment. According to Cliff, "we essentially engaged with industry, we prepared interviews and reached out to industry SMEs, conducted and documented the interviews, wrote the report and [once we] got sign off on the terminal sterilization document, we did the same thing for aseptic processing on behalf of biotech."

Cliff said that the one common denominator in all the interviews was that each participating company had its own individual method of managing and assessing sterility assurance and site location change processes that were not always traceable to prevailing Agency guidance or regulation. In his paper, he said that "from an industry perspective, this was rationalized

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2010 PDA/FDA Joint Regulatory Meeting Say Hi, Get Answers and Save at the PDA Booth

Hassana Howe, PDA

Whether you're a new PDA Member or a veteran, there are plenty of new benefits and resources to learn about at the PDA booth during the upcoming *2010 PDA/FDA Joint Regulatory Conference*.

Located near the registration counter, PDA representatives will be available to answer all your questions about conferences and training courses, as well as membership, volunteer and marketing opportunities.

Some new resources and special discounts to note include:

1. A website dedicated to the *PDA Journal of Pharmaceutical Science and Technology*
2. The latest issue of the *PDA Letter*
3. A complimentary Virtual Membership Orientation
4. A PDA Membership Benefits Guide

Stop by PDA's booth to obtain your PDA membership anniversary pin; learn about your local chapter; and receive exclusive discounts only available at the show on PDA products, including PDA/DHI Books.

Most important – Don't forget to participate in our passport raffle to win prizes sponsored by our exhibitors during the scheduled breaks!

PDA

PDA Europe Upcoming Conferences October 2010

Visual Inspection Forum

Visual inspection continues to be an important element of the manufacturing process and the quality assurance of injectable products. Product inspection provides necessary information for lot release, and, coupled with defect identification, contributes to a strategy of continuous process improvement. The meeting will provide a forum to present and discuss new developments in the field of visual inspection, including a basic understanding of the sampling and inspection process, validation of manual and automated methods and the regulatory and compendial requirements that govern them. Special attention will be given to specific inspection challenges of biopharmaceutical drugs e.g. turbid media as well as the differentiation between protein aggregates and foreign particles.

5-6 October 2010
Berlin/Germany

Pharmaceutical Cold Chain Management

Temperature Controlled Pharmaceutical Supply Chain - From Manufacturing to the End User

The 2010 PDA two day event will focus on the supply chain of temperature controlled pharmaceuticals from the manufacturer to the end user. Aspects of temperature controlled qualification and validation using new technologies will be presented. Distribution stability studies and shipping outside of label claim will be debated. A special session is planned on storage and transportation solutions for ambient, refrigerated and frozen products. Wholesalers and pharmacists will be invited to present their plans and systems for Quality Agreements, temperature alarms and distribution traceability. The attendees will hear from regulators, industry experts, and cold chain solution partners about risk management for temperature controlled supply chain.

The 2010 **NEW** two day Cold Chain Training will consist of 4 modules covering (1) Global regulatory requirements including an overview of the recently published PDA Technical Report No. 46, Last Mile: Guidance for Good Distribution Practices for Pharmaceutical Products to the End User, (2) Packaging Development, (3) Temperature Monitoring and Data Analysis, (4) Cold Chain Risk Management. All concepts will be clarified by round table discussions and case studies.

7-8 October 2010
Berlin/Germany

Conference, Exhibition: 7-8 October
New Training Course: 5-6 October

For other events see:
www.pda.org/europe

Volunteer Spotlights

Earl Zablackis, Director Analytical Method Validation, Sanofi Pasteur

PDA Join Date: 1997

Areas of PDA Volunteerism: Analytical Methods Development for Biotechnology Products Task Force member (2008 to present); and Analytical Methods Validation for Commercial Biopharmaceutical Products Task Force member (2008 to present)

Interesting Fact about Yourself: The first scientific paper I published was a taxonomic work on my discovery in the Hawaiian Island of a new species of marine red algae (*Scinaia furcata*), which I found during my Masters studies at the University of Hawaii.

Why did you join PDA and start to volunteer? I joined PDA when I first entered the biologics industry in order to get involved in a professional organization that would allow me to learn and stay current in all aspects of biologics development, manufacturing and compliance. I became a volunteer after several years as a member when I saw the announcement to convene the Analytical Methods Development (AMD) and Analytical Methods Validation (AMV) Task Forces for creating PDA technical reports in what is my area of expertise and interest. I see volunteering on these task forces as an opportunity to work with others in industry who want to collaborate to put together a clear practical approach with best practices for analytical method qualification and validation, which are key to biologics product quality.

Of your PDA volunteer experiences, which stand out the most? Working on the AMD and AMV Task Forces with colleagues from many different companies and putting together what we think will be two technical reports that will truly be beneficial guidances and reference documents for those working in analytical method development, validation and transfer.

How has volunteering through PDA benefited you professionally? Working on the two task forces has been great for me. I have been able to meet and get to know many concerned and passionate individuals from both Europe and the United States with similar interests working towards the same goals. Working on the task forces has allowed me to collaborate with others to advance best practices for analytical method development and validation. Additionally, working on these two important technical reports has been beneficial for my company as it has given me the ability to keep my company moving forward and improving our analytical development, qualification, validation and transfer processes.

Which PDA event/training course is your favorite? I really enjoy attending the Joint Regulatory PDA/FDA conference every year in order to keep up with the regulatory side of our industry.

What would you say to somebody considering PDA membership? PDA is a great organization to join, as well as to participate in. I think I am much better at my job since joining PDA and believe my working with PDA members on the task forces has allowed me to become an effective leader for analytical methods validation in my company.

Did You Know? Some Facts About PDA

If you are a new member, or even if you have been a member of PDA for a while, you might realize that our organization has a lot going on. Our staff has compiled a list of facts about PDA that might have escaped your notice and will hopefully make accessing our publications, training courses, conferences and volunteer opportunities easier.

Did You Know…

- ✓ The *PDA Letter* can be accessed online at www.pda.org/pdaletter
- ✓ You can make PowerPoint presentations from articles at the online Journal site
- ✓ 2010 marks the 64th year of PDA
- ✓ If you want to volunteer you should check out www.pda.org/getinvolved
- ✓ If you have any questions, email info@pda.org
- ✓ There are duplicates of the comments that PDA makes on guidances at www.pda.org/regualatorycomments
- ✓ TRI offers on-site training at your facility
- ✓ www.pda.org/calendar will show you courses, conferences and chapter events
- ✓ You can find a directory and contact information of PDA staff at www.pda.org/SecNav/Contact.aspx
- ✓ Your membership includes two years worth of journal articles and you can upgrade to full access of 12 years worth of research for a small fee. Please contact info@pda.org for more info
- ✓ You can sign up for email alerts at journal.pda.org. This alert will provide table of contents, article citations and customized email-based alerts for the *PDA Journal of Pharmaceutical Science and Technology*
- ✓ We want you to send feedback on the Letter. Email **Emily Hough** at hough@pda.org and tell her what you think

Volunteer Spotlights

www.pda.org/spotlight

Stefan Köhler, Director, AstraZeneca

PDA Join Date: 2002

Areas of PDA Volunteerism: Various PDA conferences in Europe; PDA's Annual Meeting; the Board of Directors (2008-2009); Science Advisory Board (member); Audit Committee (member)

Interesting Fact about Yourself: During the summer, I love to take my boat out to the Stockholm archipelago with all of my family and visit the different islands. We fish from the dingy, BBQ and just have a great time with friends and other "boat people" that we meet there. I also love to maintain my old Jaguar car and on sunny days let the top down and take my wife Lisa to a nice restaurant.

Why did you join PDA? I have always had an interest in the relationship between technology, regulatory demands and how technology could improve patient safety. During my strategic collaboration with the KTH "Royal Institute of Technology" in Stockholm, I realized it would be helpful to be involved in an independent organization focused on both regulatory and scientific issues. I learned about PDA through the Scandinavian contamination control association, R3 Nordic and realized that PDA was exactly what I was looking for–a global organization, working from a science perspective and including both industry members and regulators, that helps to define common understandings of GMP and technical requirements.

Of your PDA volunteer experiences, which have you enjoyed the most? I have enjoyed all of my volunteer work in different ways, but my time on the PDA Board of Directors was the PDA activity that I enjoyed most of all. On the board, I could work with my colleagues and the PDA senior staff to address strategic issues and to strengthen PDA for the future. From a more tactical view, the Science Advisory Board has given me the opportunity to learn from my other colleagues who share their world class scientific and regulatory experiences! PDA is the most serious global organization within the pharmaceutical sector, and working as a volunteer leader for PDA and the membership has been a great honor.

How has volunteering in PDA benefited you professionally? My PDA service has offered me many benefits, such as:

- A better strategic understanding about where the industry is heading
- Insight on how other companies are thinking in terms of certain issues
- A better understanding of other cultures
- A significantly better understanding of how the regulatory authorities are thinking
- Early visibility of issues and trends.
- An external network of industry colleagues & PDA staff
- An opportunity to affect industry technical standards through our technical reports

Which PDA conference/training course is your favorite? The PDA/FDA Conference is always interesting, and the annual meeting is excellent from a scientific and technical perspective. I am excited to see what we can achieve in Europe with the PDA/EMEA Conference.

What would you say to somebody considering PDA membership? What are you waiting for?! PDA has given me many benefits, so I would recommend it to anyone in support of their day-to-day work. PDA connects people with knowledge and experience. It has helped me a lot and I know it will help new members just as much.

2010 PDA/FDA Joint Regulatory Meeting — The Membership Committee Would Like to Welcome You to PDA

Welcome new PDA members! If you joined PDA on or after April 1, 2010, you are invited to kick-start your PDA membership by attending the New Member Breakfast hosted on site at the *2010 PDA/FDA Joint Regulatory Conference* on Monday, September 13 at 7:00 a.m.– 8:00 a.m. This is a wonderful opportunity to learn more about PDA and to meet other new members, board members and staff.

Please RSVP by August 31. For more information and to RSVP, please contact **Hassana Howe** at +1 (301) 656-5900 ext. 119 or howe@pda.org.

NOTE: You must be a full conference attendee to attend this event. RSVP is required.

Recipients of the 2009 Honor Awards

www.pda.org/2009honorawards

The honor awards have been presented to esteemed PDA members since the first award was given in 1958. It is our intention to highlight each of the 2009 Honor Award Winners in each upcoming issue of the Letter until the 2011 Annual Meeting. This month we have chosen to spotlight the individuals who were awarded the Service Appreciation Award.

Service Appreciation Award

This award is given in recognition of special services preformed on behalf of PDA

John Shabushnig, PhD

John is a long time active member of PDA. John continues to serve on the Board of Directors, Executive Committee, Strategic Planning Committee and Science Advisory Board and as the leader of the Visual Inspection Interest Group. He also serves on the USP Parenteral Products Industrial Expert Committee, the Ad hoc Committee on Visual Inspection and is a member of the American Chemical Society. John is receiving this award in honor of his contributions to the PDA Board of Directors as Chair from 2008-2009.

Louise Johnson

Louise has enjoyed a long association with PDA and is currently a member of RAQC, the Program Advisory Board and is a member of the PDA/FDA planning committee. In her association with PDA, Louise served on PDA's Board of Directors, was the Chair of the 2005 PDA/FDA meeting and a recipient of PDA's Distinguished Service Award in 2006. Louise is receiving this award in honor of her contributions to the PDA Board of Directors as a Director.

Stefan Köhler

Stefan has been a member of PDA for 10 years. In that time, he has served as a chairman for various PDA conferences in Europe and participated in a majority of committees for PDA's Annual Meetings. Stefan served on the Board of Directors from 2008-2009. Currently, he is a member of the Science Advisory Board and a member of the Audit Committee. Stefan is receiving this award in honor of his contributions to the PDA Board of Directors as a Director.

Robert Caunce

Robert has been a member of the PDA for 8 years. He has been on the PDA Australian Chapter since 2006, and in 2007, he was the President of the chapter. He is currently the Past President. Robert is an active member of the RAQC, providing regulatory updates for the Australian region. He is receiving this award in honor of his contributions to the PDA Australian Chapter as Chapter President.

Robert Buchholz

Robert has been a member of the Mountain States PDA chapter for many years and has served as President to the chapter for the past two. He is receiving this award in honor of his contributions to the PDA Mountain States Chapter as Chapter President.

Please Welcome New PDA Members

Fernanda Abujamra, Merial Saude Animal
Alpesh Agrawal, Cibavision
Mohammad Ali, Incepta Pharmaceuticals
Adrian Alston, Salix Pharmaceuticals
Nedim Altaras, Merck
Fred Arbogast, FHA Technologies
Benjamin Bernstein, MedImmune
Julie Block, Medtronic
Andy Blossfeld, BioMerieux
Annette Bojanski, Mesa Laboratories
Sven Borchert, Uhlmann VisioTec
Bonnie Brock, Sanofi Pasteur
Jim Cashman, Eli Lilly
Bruce Cummings, Pfizer
Stamatia Fasitsas, F. Hoffmann - La Roche
Wesley Few, ValSource
Yasue Fujii, Ajinomoto
Marco Fulfaro, AIFA
Alfonso Guarracino, Valsource
Tim Hanlan, Boehringer Ingelheim
Simon Hartley, Sensitech
George Hayduscko, Alk-Abello
Tyson Hector, Boehringer Ingelheim
Delvaux Hilde, Genzyme Flanders
Erik Hjorth, Sanofi Pasteur
Blake Hughlock, Stryker
Zhinhua Hung, Bureau of controlled Drugs, Department of Health, Executive Yuan
Shunji Iida, Japanese Red Cross Society
Atsushi Isoai, Chugai Pharmaceutical Company
Wesley Jackson, Covidien
Fariba Jashnian, Baxter Healthcare
Kiyoko Kaneko, Ajinomoto
Prashant Kavale, GMP Technical Solutions
Peter Knott, PMT
Sachiko Kobayashi, Daiichi Sankyo
Farid Koudssi, BioMerieux
Todd Krizelman, CSM Agency
Randall Lane, American Thermal Instruments
Miyeon Lee, Celltrion
Stephanie Levine, Eli Lilly
Maria Lofgren, AstraZeneca
Angel Lorenzo, Abbott
Shawn Martin, Genzyme
Heriberto Martinez, Commissioning Agents
Lucinda Martinez, Alcon Laboratories
Catherine Masse, Teva
Peter McNamara, Micro-Bio
Tanisha McClendon, Biogen Idec
David McGovern, GE Healthcare
Charles McNulty, Biotest Pharmaceuticals
Tetsuya Mimura, Daiichi Sankyo
Daisuke Murayama, Japan
Akira Nakaji, Ajinomoto
Toshitugu Nishino, Astellas Toyama

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How Much is Too Much? Train Your Employees Appropriately

Baltimore, Md. • October 11-15 • www.pda.org/biennial2010

Biennial Conference Committee Member Kristina R. Spitler, Almac

What would you consider a reasonable number of standard operating procedures (SOPs) for an employee to be trained on in a single day? Five? Ten? Twenty? Or would it be dependant on the complexity of the SOP?

How about 170?! Yes, when polled, more than a couple of trainers have responded that they have actually seen records demonstrating that an employee was trained on over 100 SOPs in a single day. Of course, it's absurd to think that was effective in any way, if even humanly possible, but it is a real crisis among the GxP training community. Another consideration is whether or not it is even possible for an employee to retain the content of 170 SOPs over the course of their employment? How much is too much? At what point is training a *"formalistic and useless exercise to satisfy a regulation"* **(1)**?

Common sense and experience tells us that people have limits on how much they can learn at one time. They also have a capacity on how much information they can retain over the long haul. Many regulators suggest placing a limit on how many procedures a person can be trained on in one day, which is wise advice. However, the problem isn't just that people are training too many procedures in a given day, a deeper problem is the extensive number of procedures an employee is **expected** to know, e.g., the number of procedures on the employee's training curriculum.

Tacking the problem needs to start at the root, which is the overwhelming number of procedures required for employees. You may think, "How can a trainer even imply that training should be minimized?" It is not being suggested that training be merely minimized but rather more targeted so that employees can really focus on learning more of what they need to know in order to do their jobs effectively.

The Bare Necessities

It's important to get back to basics and remember why employees need training to begin with. To ensure that personnel are "qualified" to do assigned tasks, which in turn ultimately ensures that safe product is produced, is a formidable goal. United States and international regulations, as well as guidance documents, **(2)** seem to echo a common sentiment regarding training:

1. Employees must have the proper education, training and experience, or any combination thereof
2. Personnel should be enabled to perform assigned functions
3. Employees need training in particular operations that they performs
4. GMP training should be provided with sufficient frequency
5. Training should not be a one time event, it should be continuous
6. Training effectiveness should be assessed
7. Training needs should be identified
8. Programs should be approved
9. Training records should be kept
10. Quality concepts should be discussed for employee awareness

It all sounds pretty simple, and it makes good sense, so why is training historically listed in the top ten reasons companies are cited with 483s by the FDA? Of course, companies desire to comply with regulations and have well trained staff; yet, they often don't know where to begin, short of making a long list of requirements and checking them off one by one.

Breaking It Down

Analyzing the training **need** and identifying **content** is a key step. However, taking the content and mapping it to the appropriate roles within the organization seems to be a challenge for a lot of training departments and managers.

Figure 1

	What	Who
Task 1		
Task 2		
Task 3		

An easy way to analyze training needs is to break a task into subtasks and identify who should perform it

One way to tackle the task is to do a thorough task analysis. Identify the task being performed and break it down into subtasks (See **Figure 1**). Then consider who will be involved in performing or verifying that task. Consider how other people may need to be involved and why based on the various job **functions** and **specific operations** within the task or process. Consider if the involvement is simply "for your information" and whether or not it is even necessary for certain personnel. If the answer is "no," then spare them the requirement.

Next, think about how intensely the various personnel need to comprehend, understand or perform the task or process.

Learning can be qualitatively expressed as different levels of thinking, according to **Benjamin Bloom** who developed Bloom's Taxonomy in the 1950s.**(3)** According to Bloom, learning can intensify in levels based upon the objective of the learning experience. If an employee simply needs

to remember or recall a fact or topic, he or she would only need to receive training with sufficient intensity to achieve the "Knowledge" level. If a different operator needs to perform the procedure or "apply" the procedure in particular operations, then he or she would need to receive training with sufficient intensity to achieve the "Application" level (See **Figure 2**).

Just because six different departments are mentioned in an SOP does not mean that all of those departments will have the same training need. An efficient approach is to have training "levels" as a differentiation for training needs. For example, an A, B, C approach can be used. The A level of training could be defined as the "Awareness" level, indicating that staff only need to have an awareness or recall of the process but will not be involved in performing the process. With this type of training need, written assessments/tests are not generally warranted.

The B level of training, the in "Between" stage, entails comprehension and some application of the process at an appropriate time. A written assessment or questionnaire is a suitable way to measure this level of understanding.

The C level of training may be defined as "Competency" based training requiring a written assessment, as well as demonstration of proficiency with the task. This proficiency can be evaluated by approved trainers using a checklist to score appropriate behaviors or even by evaluating simulations of actual processes.

For the more risky processes, the training may warrant multiple observations of the task, followed by assistance with the task and ultimately a trainer approving the independent performance of the task.

Figure 3

SOP#	SOP Title	Job 1	Job 2	Job3
SOP123.01	Training Topic or SOP Title	B	A	C
SOP456.01	Training Topic or SOP Title	A	C	B
SOP789.01	Training Topic or SOP Title	C	A	C

A matrix can be tailored to a department's specific training needs

A matrix can be developed to map various SOPs to departments at different levels (See **Figure 3**).

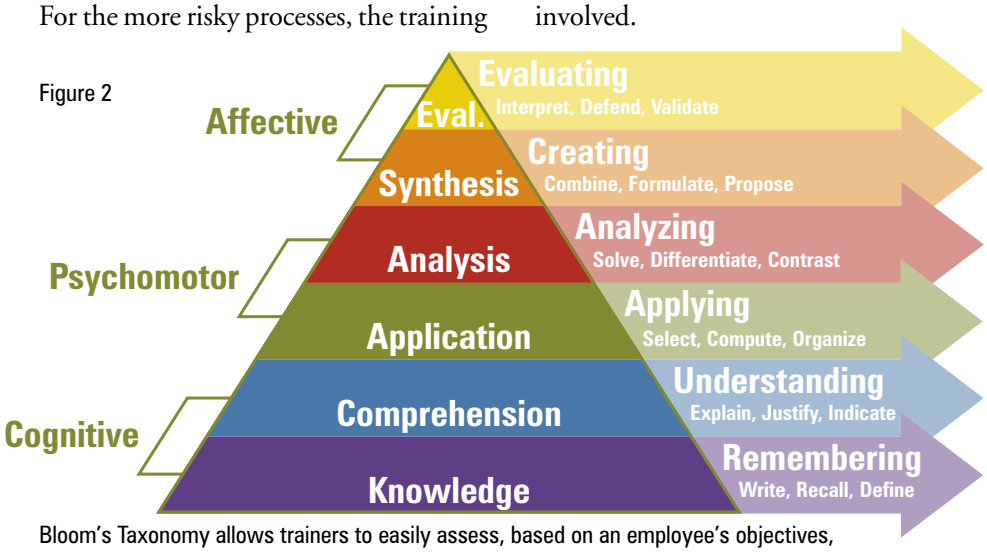
By identifying the appropriate level of learning, managers and trainers are well on the way to developing a targeted training curriculum for each employee that is more efficient and manageable.

The level of learning can be also be associated with an educational domain. There are three general educational domains: Cognitive, Psychomotor and Affective (See **Figure 4**), which are sometimes referred to as K, S and A: Knowledge, Skills and Attitudes.

The Cognitive domain (or Knowledge) involves mental skills and areas of knowledge, while the Psychomotor domain (or Skills) involves physical abilities. The Affective domain (or Attitudes) involves education that encourages emotional growth or a change in perception.

The style of instruction should vary with the level of learning and the domain involved.

Figure 2



Bloom's Taxonomy allows trainers to easily assess, based on an employee's objectives, what level of training to provide

An informational topic, which must be relayed to the "Knowledge" or "Comprehension" level, may be well served with an e-learning module followed by a computerized assessment. The Affective domain is tied to the "Synthesis" or "Evaluation" level. This topic requires the instructor to motivate the trainees to see the benefits of the new system and be willing to take on the learning curve to attain those benefits. Psychomotor skills, which must be understood to the "Application" or "Analysis" level, generally require instructor led sessions with hands-on exercises with some type of "on the job" training reinforcement.

Once the level, domain and delivery method is determined, it is important to consider how the learning will be evaluated. How will the acquisition of the knowledge, skill or attitude be observed and measured? A variety of assessment tools can be developed ranging from written assessments or "tests" to demonstrations involving a "checklist" of objectives, similar to a driving test when obtaining a driver's license. Whatever assessment tool is used, it should match the learning objectives with appropriate intensity. For example, it's not vital to have an employee demonstrate a process and be scored on a checklist if the employee only needs to have a general knowledge of the process and will never actually "perform" the task, e.g., an "A" level procedure.

Target Practice

By carefully analyzing the learning objectives in the fashion described and identifying targeted training requirements for each job type, it's possible to achieve more by training less. When training is more appropriately matched to the learning needs of the employee, valuable training time will be spent on the processes with the most impact, ensuring an efficient and effective use of resources.

Figure 4

	What	Who	Depth Bloom's Level	Domain KSA
Task 1				
Task 2				
Task 3				

This educational domain allows instructors to assess what level of training to provide to trainees

Attend the 2010 PDA Biennial Training Conference October 11-15 in Baltimore, Md. to learn more about the topics presented in this article. For more details about the conference and to register, please visit www.pda.org/biennial2010.

References

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2. Code of Federal Regulations – Title 21, Food and Drug Administration Department of Health and Human Services, Subchapter D—Drugs for Human Use, U.S. FDA, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=312&showFR=1
3. Bloom's Taxonomy, Wikipedia, en.wikipedia.org/wiki/Taxonomy_of_Educational_Objectives

Helpful Resources

1. United States Regulations 21 CFR §211.25, §58.29, §606.20, §820.25; U.S. FDA, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312
2. Division of Manufacturing and Product Quality, about FDA, U.S. FDA, www.fda.gov/cder/dmpq

European Union Regulations

1. Rules and Guidance for Pharmaceutical Manufacturers and Distributors – (orange guide) Ch 2.8 – 2.12, MHRA, www.mhra.gov.uk/Publications/Regulatoryguidance/Medicines/Othermedicinesregulatoryguidance/CON2030291
2. ICH Q7A, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Personnel Qualifications (3.1), ICH, www.ich.org/cache/compo/2760254-1.html

Learn About Viral Detection, Control Measures at Workshop

Bethesda, Md. • December 1-3 • www.pda.org/adventitiousvirusworkshop

Program Planning Chairs Mike Wiebe, PhD, Quantum Consulting; Patricia Hughes, PhD, U.S. FDA; and Arifa S. Khan, PhD, U.S. FDA

The *PDA/FDA Adventitious Viruses in Biologics: Detection and Mitigation Strategies Workshop* is being organized currently as a result of recent viral contamination events. This workshop is intended to encourage modernization in industry with respect to viral detection and control measures. Gaps in our current ability to detect, control and clear adventitious viruses; the availability of emerging technologies in areas where gaps exist; and CGMP expectations for adventitious virus detection and control, as well as consequences for noncompliance will be discussed.

This workshop will be held on December 1-3 in Bethesda, Md., and current and updated manufacturing practices and processes designed to prevent adventitious viruses in biologics will be reviewed. It will also highlight the U.S. FDA's regulatory expectations for product quality and purity with respect to adventitious agents.

This three day workshop will also provide focus on:

- Current industry standards
- Review of viral contamination in biologics and case studies
- Gaps in overall testing strategies and emerging technologies for novel virus detection
- Best practices to mitigate virus contamination and evaluation of the risk to patients
- Barrier and inactivation strategies for control of raw materials
- Application of concepts presented in ICH Q7 and Q10 as they relate to the prevention and detection of viral contamination in production processes and approaches

The workshop will provide an engaging forum for regulatory, industry, and academic colleagues to discuss and integrate current and emerging strategies for controlling virus contamination for product safety.

Be sure to keep your eye on the Letter for future announcements about this workshop.

An Update on Risk Management of Aseptic Processing

Bethesda, Md. • November 15-16 • www.pda.org/asepticprocessingworkshop

Workshop Co-chair Hal Baseman, ValSource

Aseptic processing of sterile drug and healthcare products continues to be a subject of considerable attention by our industry and its regulators. New guidance and new technologies have resulted in the need for innovation and change in how we safely and effectively manufacture these products. Reacting to the need for change alone can be problematic. The industry must initiate and continue an open exchange among regulators, scientists and suppliers to better understand the technology and regulatory developments and facilitate the needed changes in our approaches, Technical trade organizations, such as PDA can help by holding meetings and conferences which bring these parties together in an atmosphere of cooperative dialog.

In May of 2008, PDA held an important interactive meeting in Bethesda, Md. on aseptic processing and risk management. The purpose of the meeting was to identify challenges facing our industry related to effectively and efficiently manufacturing sterile drug products using aseptic processes. That meeting brought together leading representatives and experts from industry and the FDA to discuss approaches for recognizing and addressing risk to patient safety in designing and performing aseptic processes. Throughout the meeting, questions were raised and debated regarding the use of new technologies and methods for aseptic processing and the inherent challenges to recognizing, and meeting the need for change and improvement. This change in regulatory expectation and acceptance of technological advances was acknowledged as an essential requirement. The conference presented risk assessment as a useful tool for identifying, mitigating and communicating contamination risk with the objective of enhancing aseptic process control. The conference ended with a lively panel discussion and the promise to follow up with a second conference to further explore meeting the many challenges uncovered.

This November 15-16, PDA will follow up that meeting. The *2010 Aseptic Processing: Issues and Approaches Conference* will again be held in Bethesda, Md. The meeting will review contemporary practices for the conduct of aseptic processing and address topics and concerns related to the latest aseptic processing technologies. Sessions will again include presentations by regulatory and industry representatives, but the emphasis will shift from *identifying challenges* that could result in risk to *meeting those challenges*. To that end, the meeting will discuss topics related to parametric release, post aseptic lethal treatments, sterility by design, control of interventions, quality systems, aseptic process simulations and validation, manual aseptic processing, process modeling, as well as related topics.

The primary objective of this meeting is to explore the approaches needed to transition aseptic processing to better fulfill the operational challenges with technological approaches; exploring the use of new methodologies and adaption of existing methodologies; and advancing the dialog between industry and regulators on the steps necessary to improve production processes and assure continued quality of aseptically produced sterile products.

The questions this meeting hopes to answer include:

- How should firms design process control programs which will effectively meet the FDA current cGMP requirements with technologies that at times transcend the existing control paradigms?
- How to reconcile FDA's draft Process Validation Guidance with the validation requirements for aseptic processes?
- Are Post Aseptic Lethal Treatments a reasonable and feasible approach for mitigating microbiological contamination related risk for sterile products?
- How can firms design aseptic processes and quality systems to better assure process control and product sterility?
- What methods can firms use to identify, evaluate, and reduce the impact of human interventions on sterile products?
- Is there a continued role for manual aseptic processing in light of technology changes?
- What are the new technologies and issues on the horizon which can further enhance sterile product manufacture and how can companies prepare for their effective use and impact?

It is important that aseptic processing professionals take an active role in the addressing the changes taking place in our industry. It is our individual and collective responsibility to manufacture sterile products in as safe a manner as possible. We must become aware of, and perhaps influence, the direction of change for further improvements where necessary. We encourage you and your colleagues to attend and participate in the discussions and decisions which will result from this meeting and to continue taking an active role in its outcome.

Tails from the Trail, continued from page 46

by the argument that there is no one right way of doing this."

Cliff concluded by telling the audience at the meeting that the key outcome of his investigation was that the use of a comparability protocol under 21 CFE314.70 (e) was a feasible and acceptable approach, OPS preference being that information be submitted in MAPP 5040.1 format. He also stressed that the assignment did not extend to CBER-regulated products.

End User's Needs Highlighted at Syringe & Device Meeting

Las Vegas, Nev. • October 18-21 • www.pda.org/prefilled2010

Conference Co-chairs Rey Chern, PhD, Merck Sharp & Dohme and Brigitte Reutter-Haerle, Vetter Pharma International

We live in an era of ever-accelerating change. The world of medicine includes the rapid evolution of technologies, market trends and regulatory requirements as they pertain to transforming pre-filled drug-delivery systems. Keeping abreast of new developments is no longer sufficient. We must stay *ahead of the curve*, so we can be ready for the future–and help to shape it.

To support us in meeting this challenge, this year, the *2010 PDA Universe of Pre-filled Syringes and Injection Devices* will examine the advanced needs of pre-filled syringes and autoinjectors. In particular, we will spotlight the needs of the end customer, the patient and the person who administers the medicine, which could be the patient or the care giver.

Plenary sessions during this two-day conference will cover topics such as:

- Intimate relationship among national health policy, medical needs and the role of injection devices and innovation
- Business processes for development and regulatory registration of the drug-device combination product, accounting for human factors and clinical trials
- Quality issues and infrastructure for supporting the franchise
- New technologies and trends in manufacturing processes for components and form-fill
- Case studies covering development and manufacturing, regulatory and marketing topics
- Critical attributes and risk management of injection devices
- Regulatory and compliance topics
- New primary containers with an emphasis on plastic syringes
- New safety devices and delivery systems

Two parallel tracks of sessions, led by global experts, will enable participants to choose from a variety of current and compelling topics.

Additional exciting offerings include:

- Two breakfast sessions covering new developments in safety devices and invasive drug deliveries
- Four poster sessions and networking opportunities with industry experts
- An exhibit hall of current and future products or technologies
- Two new PDA Training and Research Institute courses focused on the development and manufacture of prefilled systems

Whether you are new to the field or an industry veteran, you will take away practical knowledge to put immediately into use, as well as networking with new colleagues and contacts. We invite you to participate in the *2010 PDA Universe of Pre-Filled Syringes and Injection Devices*, October 18-21, in Las Vegas, Nev. We hope to see you soon!

2010 PDA/FDA Joint Regulatory Meeting FDA Commissioner Hamburg to Outline Initiatives

Opening Plenary Session: FDA's Initiatives
Margaret Hamburg, M.D., Commissioner, U.S. FDA

This opening plenary provides a unique opportunity to hear the Commissioner present the current and future focus of the FDA.

Maintain Quality in Midst of a Merger at PDA/FDA Session

Washington, D.C. • September 14 • www.pda.org/pdafda2010

Conference Co-chair Sue Schniepp, Antisoma

The date for the *2010 PDA/FDA Joint Regulatory Conference* is drawing near. Scheduled for September 13-15 in Washington D.C., this year's conference theme focuses on how companies can maintain quality standards while dealing with mergers, acquisitions and new emerging regulations. In today's environment, companies are combining workforces and product portfolios to be able to compete in a multinational market place. The challenge for these organizations are to integrate complex quality systems while maintaining compliance to existing and emerging regulations from domestic and international regulatory authorities.

Many business and quality challenges face both the acquired company and the acquiring company following an acquisition. The adoption and effective deployment of a common quality management system across the entire company is often a goal that is not adequately achieved. The session, titled, "Case Studies – Business and Quality Systems Implications in a Post Acquisition Setting" will feature **Winston KC Lam**, **Jim Bedford** and **Mark Ehlert**. Each will offer a unique perspective on the topic of mergers and acquisitions.

This session will examine the challenges a medical device manufacturer faced with an accumulation of eight separate companies with different quality systems following multiple acquisitions. It will also offer insights into the challenges facing Merck and Schering-Plough as they combined their businesses. The Hospira separation from Abbott and the Mayne acquisition will also be addressed.

The speakers have a lot of experience with the topic they are presenting. Bedford, Ehlert and Lam have all played prominent roles in mergers throughout their careers.

Bedford currently is a Vice President at Regulatory Compliance Associates, Inc. and leads the Mergers & Acquisition practice. Before joining RCA, Jim managed the Midwest Life Science practice for BearingPoint. Jim also led several large mergers and divestitures for Baxter Healthcare and Caremark International.

Ehlert is currently President and Owner of 315 Ventures, Ltd., a company devoted to bioscience and medical device startup companies and due diligence activities associated with mergers and acquisitions. Prior to establishing 315 Ventures, Mark was with Baxter Healthcare from 1975 until joining Allegiance Healthcare in 1996 upon their spinoff from Baxter. At Allegiance, Mark was a Corporate Officer responsible for Quality, Regulatory Affairs, EH&S and Research and Development functions. He managed those areas for the Medical Device Manufacturing businesses of Cardinal until the end of 2003 when he left Cardinal to help with the spinoff of Hospira from Abbott Laboratories. Mark was a member of the Senior Management team that created Hospira and served as the Corporate Vice President of Quality and Regulatory Affairs. At the end of 2006, he headed the Integration team until his retirement upon the acquisition of Mayne Pharma by Hospira.

Lam currently is a Principal with Strategic Advisory Services LLC, a business development consulting firm focused on the life sciences and healthcare sectors. Prior to this, he was the Group Vice President and Associate General Counsel, Global Pharma Business and Business Development & Strategic Alliances for the Schering-Plough Corporation. In this role, he provided strategic and legal leadership for Schering-Plough's business development, licensing and strategic alliance initiatives. Among other things, Winston was one of the leaders of the senior management team that executed and managed Schering-Plough's $16 billion acquisition of Organon Biosciences Nev., the human and animal health businesses of Akzo Nobel, and later, the $45 billion Schering-Plough–Merck merger. He was also one of the leaders of the integration process and team in each of the transactions.

So, if you are interested in learning about the trials and tribula-

tions of merging companies and quality systems from experienced individuals who have participated in a number of mergers and acquisitions, you should plan on coming to this session at the PDA/FDA Joint Regulatory Conference.

Minimize Patient Risk at Extractables & Leachables Workshop

Washington, D.C. • September 15-16 • www.pda.org/eandlworkshop

Planning Committee Chair Diane M. Paskiet, West Pharmaceutical Services

A systematic approach to the selection and control drug product contact materials can minimize the risk of causing harm to patients as a result of the potential interaction with packaging, processing materials or delivery devices. The safety and/or efficacy of a drug product may be compromised if a comprehensive knowledge base of extractables has not been established and linked to leachables in relation to critical aspects of storage, manufacture and delivery of the drug product.

Regulatory initiatives are transforming with the implementation of ICH Q8, Q9 and Q10 and suitability of product contact materials is a critical issue to be addressed in the drug product design space and management of risk. Appropriate information gained from properly conducted extractable and leachable studies will support the drug product life cycle from drug development through scale up and from commercialization to product discontinuation.

The PDA/FDA Joint Regulatory post-conference workshop, *Extractables and Leachables Workshop: Impact on the Quality of Packaging, Process Materials and Delivery Systems* will feature presentations related to the impact to the quality of packaging, processing materials and delivery systems. By attending this workshop, you will learn how these studies can be adapted in light of the *GMPs for the 21st Century*. The presentations will touch upon the following topics:

- Considerations for Contact Materials used in Biologics, Approaches to Safety Assessments
- Extractable Leachable Challenges in a Global Environment
- Practices for Change Control Strategies
- Management of the Container Closure Supply Chain
- Strategies for Selection and Control of Drug Product Contact Surfaces
- Illustrations of Extractables
- Leachables Studies in Combination Products

Required information on drug product contact materials can vary worldwide and integration of multinational expectations poses additional considerations in determining material suitability. Learn about the issues of compliance from a global perspective.

Drug product contact materials vary not only in types of materials but types of products and function of contact materials. The impact to patient safety has additional challenges for the biopharmaceutical industry, and **Ingrid Markovic**, PhD, Expert Review Scientist, CDER, U.S. FDA, will provide insight on leachables in biologics.

Material qualification is multifaceted and inevitably some degree of change may occur to the drug product contact materials and methods of manufacturing over the drug product life cycle. This can be due to the supply of materials or opportunity for improvements. A major topic of interest in the conference is sure to be the practices for implementation of change and how to manage re-qualification.

Extractables in drug product contact materials, monitoring and control is rooted in the supplier knowledge and understanding of upstream controls. Sources of raw materials need to be available and qualified to ensure a consistent product. Strategies to manage the supply chain and assessing the impact of raw materials change will also be discussed.

Case studies will demonstrate compatibility as applied to pre-filled syringes and ophthalmic dosage forms along with strategies to minimize the risk of selecting an inappropriate container closure system. Safety assessments are essential to the selection process and approaches for toxicological assessment of leachables will be shown. A case study of an extractables and leachables qualification process will also be given.

Evaluations of extractables/leachables in combination products have a unique perspective in that both drug contact and patient contact will have a critical impact on the study. Examples representative of both drug and device as the primary mode of action will be illustrated. Presentations from regulators in CDRH and CDER will provide opportunities for participants to understand some of the critical differences.

A special price will be offered to individuals who register for the Extractables and Leachables Workshop for the third and last day of the *2010 PDA/FDA Joint Regulatory Conference*. These conference sessions will inform participants about regulatory updates of FDA's current hot topics and a center direction initiatives will be presented from the Agency leaders at CDER, CBER, CDRH, CVM and ORA. To register, please contact Patresa Day at 301-656-5900 ext 115 or via e-mail at day@pda.org.

Faces and Places: Cold Chain Management Conference

Pharmaceutical Cold Chain Interest Group Updates

(l-r) Bob Seevers, Eli Lilly; Rafik Bishara; Geoffrey Glauser, Pfizer; Rosa Motta, U.S. FDA

Security for Temperature Controlled Pharmaceutical Products

(l-r) James Dowden, F. Hoffmann-La Roche; Sean E. O'Neill, Genentech; Marc Rossi, TSA; Thaddeus Poplawski, U.S. FDA

Cold Chain at the Wholesaler and Retailer

(l-r) Claude Jolicoeur, McKesson Canada;
Chris J. Anderson, Cardinal Health; John Howells, HDMA

ISTA Standards for Temperature-Controlled-Products

(l-r) Ed Church, ISTA; William Pelletier, University of Florida; Brian Wallin, Amgen; Rod Derifield, EnviroCooler

Radio Frequency (RF) Energy vs. Biopharmaceuticals and Case Studies of Practical Uses of RF in the Pharma Supply Chain

(l-r) Dave Ulrich, Abbott Laboratories; Arminda Montero, Abbott Laboratories; Scott Rasmussen, Abbott Laboratories

Good Cold Chain Distribution Practices

(l-r) Paul Harber, Eli Lilly; Nishchal Chudasama, Bristol Myers Squibb; Christofer Matney, Indianapolis Airport Authority

Risk Mitigation

(l-r) Maryann Gribbin, Johnson and Johnson; Vincent Porzio, Merck; Boriana Cavicchia, American Red Cross

Cold Chain Partners - Innovative Solutions

(l-r) Karl Kussow, FedEx Custom Critical; Eric Lindquist, Entropy Thermal Management Technologies; Jennifer Veerasamie, CIBA Vision Sterile Manufacturing; Emilio Gerry Marasigan, SNC Lavalin

Faces and Places: Pharmaceutical Supply Chain Workshop

Call to Action Session

(l-r) Janet Woodcock, U.S. FDA; Barbara Mary Allen, Eli Lilly; Edwin Rivera Martinez, U.S. FDA; Deborah Autor, U.S. FDA; Martin VanTrieste, Amgen

Improving Analysis and Testing Strategies and Technologies

Steven Wolfgang, U.S. FDA

Benchmarking: Beyond Pharma Industry

(l-r) Barbara Mary Allen, Eli Lilly; Karl Kussow, FedEx Custom Critical; Chuck Forsaith, Purdue Pharma Technologies

Closing Keynote

(l-r back row)Edwin Rivera Martinez, U.S. FDA; Barbara Mary Allen, Eli Lilly; Michael Levy, U.S. FDA; Eric Berg, Amgen; Gordon Munro, Watson Pharma.
(l-r front row) Deborah Autor, U.S. FDA;Ilisa Bernstein, U.S. FDA; Rick Friedman, U.S. FDA; Zena Kaufman, Abbott Laboratories

Monitoring and Responding to Signals in the Market Place

Zena Kaufman, Abbott Laboratories; Frank Perrella, U.S. FDA

Enhancing Supplier Quality Management

Eric Berg, Amgen

Edwin Rivera Martinez, U.S. FDA; Gwyn Murdoch, Eli Lilly; Richard Levy, PDA

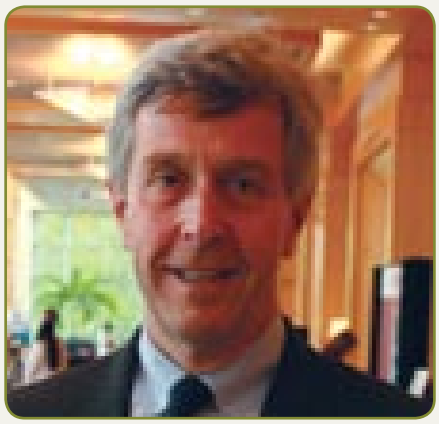
Enhancing Drug Product Distribution Supply Chain Controls and Use of Sterilization, Track and Trace, ePedigree

(l-r) Ilisa Bernstein, U.S. FDA; Michael Levy, U.S. FDA; Gordon Munro, Watson Pharmaceuticals

PDA President Richard Johnson speaks with FDA's Deborah Autor

Faces and Places: 2010 PDA/FDA Vaccine Conference

Role of Vaccines in Healthcare: Current State and Challenges

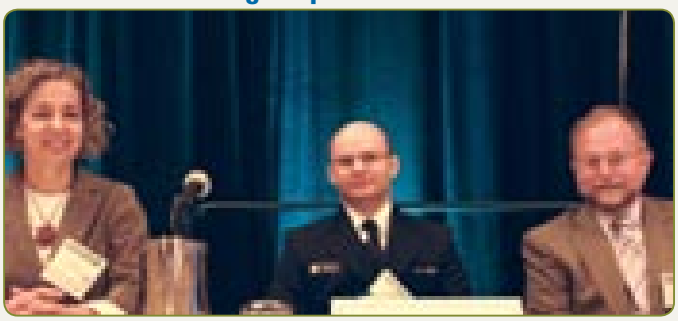


(l-r) Bruce Gellin, Department of Health and Human Services; Rebecca Devine; John W. Boslego, Path; Norman W. Baylor, U.S. FDA

Expanding Role of Vaccines in Healthcare: A Vision of the Future

(l-r) Amy Scott Billman, GlaxoSmithKline; Kathryn Zoon, NIH; Raj K. Puri, U.S. FDA

Non-Clinical Testing Requirements



(l-r) Jane Halpern, Genocea Biosciences; Jeremy L. Wally, U.S. FDA; Steven Pincus, Novavax

Establishing Modern Vaccine Processes

(l-r) Beth Junker, Merck; Mike Kosinski, Merck; Rebecca Devine

Novel Expression Systems

(l-r) John Finkbohner, MedImmune; Keith Peden, U.S. FDA; William M. Egan, Pharma Net Consulting

Bulk Manufacturing & Aseptic Processing Issues

(l-r) Benjamin Mabile, GlaxoSmithKline; Jefferey Jones, Emergent Biodefense Operations; Anthony Luttrell, Raland Technologies

Viral and DNA Clearance

(l-r) Julia Lukas, Merck Sharp & Dohme Corporation; Rebecca L. Sheets, NIH; Arifa Khan, U.S. FDA

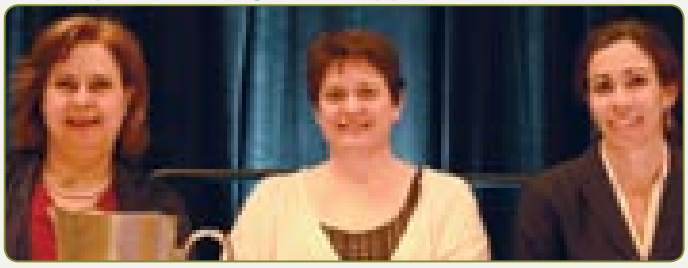
Supply Chain Complexity/Cold Chain

(l-r) Anthony Luttrell, Raland Technologies; John Tabor, National Retail Systems; Charles W. Nicholls, Jr., MedImmune

Novel Delivery Systems

(l-r) Kirsten Vadheim, BioCompliance Consulting; Gregory M. Glenn, Intercell; Tarek Hamouda, NanoBio

Demonstrating Product Comparability: Development through Post-Approval



(l-r) Elizabeth Leininger, Elizabeth Leininger Consulting; Robin Levis, U.S. FDA; Nancy Kavanaugh, MedImmune

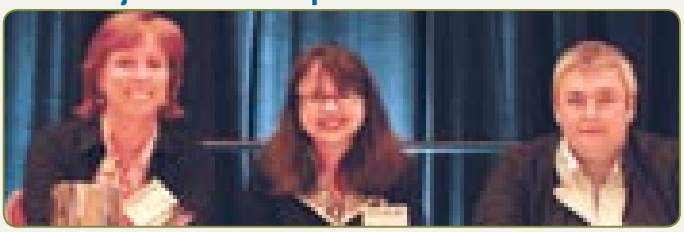
Process Validation

(l-r) Stephen Lubeck, Novartis; Chiang Syin, U.S. FDA; Manish Vyas, Novartis

Modular Flexible Facilities

(l-r) Geoff Hodge, Xcellerex; John Hyde, Hyde Engineering & Consulting; Maik Jornitz, Sartorius Stedim

Novel Adjuvants Development Considerations



(l-r) Amy Scott Billman, GlaxoSmithKline; Carmen M. Collazo, U.S. FDA; Nathalie Garcon, GlaxoSmithKline

Analytical Methods

(l-r) Michael VanDerWerf, GlaxoSmithKline; Earl Zablackis, Sanofi Pasteur; Mark Schenerman, MedImmune; Phillip R. Krause, U.S. FDA; Chiang Syin, U.S. FDA; Tim Schofield, GlaxoSmithKline; Robert Sitrin, Merck

Lessons Learned: Last couple years… Last Couple days

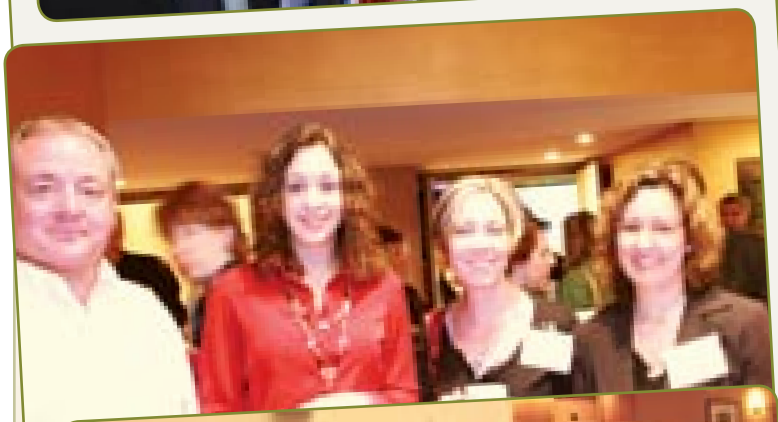
(l-r) James G. Kenimer, Biologics Consulting Group; Robin Robinson, Department of Health and Human Services; Peter A. Patriarca, Biologics Consulting Group; Bernardus N.M. Machielse, MedImmune

Biological Product Deviation Reporting (BPDR)

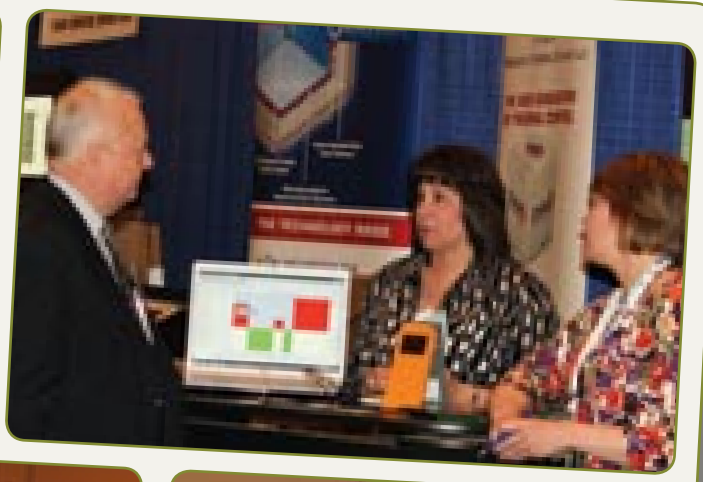
(l-r) Julia Lukas, Merck Sharp & Dohme; Sharon L. O'Callaghan, U.S. FDA

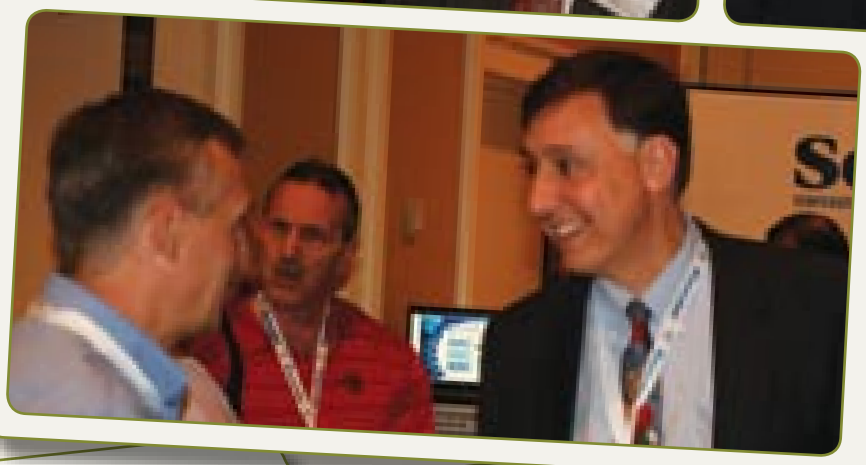
Networking at the PDA Meetings and Conferences

Supply Chain



Cold Chain





Vaccine Conference

2010 PDA/FDA Joint Regulatory Meeting Stay in Compliance: Attend A TRI Course at PDA/FDA

Washington, D.C. • September 16 • www.pdatraining.org/pdafdacourses

Stephanie Ko, PDA

With the continuing likelihood of budget cuts drastically affecting the funds available for training, it is important to make the most out of your traveling opportunities. For the *2010 PDA/FDA Joint Regulatory Conference*, you have the chance to double your benefits by attending both the upcoming conference and a training course. By staying only one extra day, you can receive in-depth training by taking one of six courses being offered by PDA's Training and Research Institute. These courses were especially chosen to match the interests of those attending the *2010 PDA/FDA Joint Regulatory Conference*, so it's worthwhile to consider what TRI has to offer.

TRI has worked with a former FDA investigator in developing a new course. **"A Former FDA Investigator's Perspective on Conducting Effective Deviation Investigations, Root Cause Investigations, Corrective and Preventive Actions (CAPA)"** will focus on the instructor's insights into the key elements that must be considered when conducting deviation investigations, proposing corrective actions and ensuring your preventive actions are effective, following a quality systems approach.

Due to popular demand from last year's conference, we are once again offering the course that more than doubled our projected number of attendees: **"Quality by Design for Biopharmaceuticals: Concepts and Implementation."** What's the draw? Successful implementation of QbD requires that critical concepts be put in place during and throughout the design and manufacture of biotech products. Participants will be able to explain these concepts and define the role they play in QbD implementation.

Addressing the challenging role and responsibilities of the GMP auditor, you can learn to construct and operate effective audit plans with **"Establishing and Operating an Effective GMP Audit Program."** Ensure your firm maintains a solid compliance posture by demonstrating how an audit program should be developed, operated and maintained, as well as factoring in the auditing skills and interpersonal skills critical to success.

The pharmaceutical industry, now more than ever, faces demanding requirements for better quality assurance and cost reduction. To develop a quality product at low cost, consider taking, **"The Quality System: Design, Implementation, Evaluation and Management of Processes,"** which will identify the characteristics of an efficient and effective process design. Come to the training with your process problems and learn to implement the redesign process, addressing the change and cultural impediments in doing so.

Are you an API manufacturer? Identify and explain key aspects of EU and US GMPs by attending, **"Essentials of US and EU GMPs for Manufacturers of Active Pharmaceutical Ingredients (APIs)."** Participants will learn specifically what is expected from manufacturers and will be able to present pragmatic ideas for ICH-Q7 implementation, the international standard of Good Manufacturing Practice for APIs. Topics include supply chain elements such as materials management, storage and distribution as well as quality management, validation, and contract manufacturers.

Finally, evaluate your training program and examine various methods of avoiding processes that lead to FDA corrective actions or warnings by taking, **"Making the Grade with the FDA."** This course puts into focus the FDA Guidance, *GMP Quality System Approach to Current Good Manufacturing Practice Regulations*, which specifies critical aspects of training programs that will be discussed.

The demand is high and seating is limited so it's important to plan ahead and register as early as possible. For more detailed information about these courses and more, please go to www.pdatraining.org/pdafdacourses.

Can't attend a course following the *2010 Joint Regulatory PDA/FDA Conference*? Consider contacting us for in-house training, and we'll bring the course directly to you and your colleagues, saving your company time and money.

PDA Welcomes New Members, continued from page 51

Paul Nolan, GE Healthcare
Eileen Ohlander, Allergan
Yoshiharu Otoyama, Ajinomoto
Nicholas Pelliccione, Aeterna Zentaris
John Peterson, Genentech
William Present, Celgene
Roberta Rennie, Portola Pharmaceuticals
Hernan Roa, Gemepe
Teresa Roberts, Biogen Idec
Brian Sampson, Medical Instill Technologies
Gerson Santiago, GS Validation Services
Adrienne Schmidt, Sigma-Aldrich
Julie Seiffert, Three Rivers Pharmaceuticals
Mark Severns, Rapid Micro Biosystems
Shireen Shuqum, Hikma Pharmaceuticals
Scott Sieler, Hospira
Tanima Sinha, U.S. FDA
Amy Stancil, Covidien
Mark Steinberg, Boehringer Ingelheim
Katsuhito Takahashi, Osaka Medical Center
Jordan Tapia, RS Calibration
Jonathan Tice, ImClone Systems
Faustino Toba, Dr Py Institute
Michael Travis, Front Range Laboratories
Geoff Trommater, Catalent Pharma Solutions
Vince Woodall, VelQuest
Feng Xingfu, Huadong Medicine Ningbo
Hisako Yamamura, Osaka Medical Center
Danielle Zadnik, GlaxoSmithKline
Keren Ziv, Rafa Laboratories

If your information appears inaccurate in this list, please visit www.pda.org to update your profile or email changes to info@pda.org.

PARENTERAL DRUG ASSOCIATION TRAINING AND RESEARCH INSTITUTE (PDA TRI)

Upcoming 2010 Laboratory and Classroom Training for Pharmaceutical and Biopharmaceutical Professionals

Save **10%** by registering early!* ***Become a PDA member and save even more on your course registration!***

July 2010

20-23: Downstream Processing: Separations, Purifications and Virus Removal
Bethesda, Maryland
www.pdatraining.org/downstream

26-30: Basic Microbiology for Aseptic Processes
Bethesda, Maryland
www.pdatraining.org/basicmicro

August 2010

2-6: Rapid Microbiological Methods
Bethesda, Maryland
www.pdatraining.org/rapidmicro

10: Writing Standard Operating Procedures – *New Course*
Bethesda, Maryland
www.pdatraining.org/writingSOP

11: Six Sigma in Process Validation – *New Course*
Bethesda, Maryland
www.pdatraining.org/sixsigma

16-20: Aseptic Processing Training Program - Session 4*
(Week 2: September 20-24)
Bethesda, Maryland
www.pdatraining.org/aseptic

SOLD OUT
Seats Available in Session 5: October 18-22 and November 8-12

24-26: Developing an Environmental Monitoring Program
Bethesda, Maryland
www.pdatraining.org/DEMP

26-27: Application of Disposables in Biopharmaceutics
Bethesda, Maryland
www.pdatraining.org/disposables

30-September 1: Pharmaceutical Water System Microbiology
Bethesda, Maryland
www.pdatraining.org/watermicro

September 2010

16: PDA/FDA Joint Regulatory Conference Course Series
Washington, DC
www.pdatraining.org/PDAFDAcourses

- Quality by Design for Biopharmaceuticals: Concepts and Implementation
- A Former FDA Investigator's Perspective on Conducting Effective Deviation Investigations, Root Cause Investigations, and CAPA – *New Course*
- The Quality System: Design, Implementation, Evaluation and Management of Processes
- Making the Grade with the FDA
- Essentials of US and EU GMPs for Manufacturers of Active Pharmaceutical Ingredients
- Establishing and Operating an Effective GMP Auditing Program

28-29: Developing the Regulatory Rationale for the Reduction of Environmental and Utility Testing within an Environmental Monitoring Program – *New Course*
Bethesda, Maryalnd
www.pdatraining.org/RREM

30-October 1: Denver Course Series
Denver, Colorado
www.pdatraining.org/denver

- What Every Biotech Startup Needs to Know about CMC Compliance
- Risk Management for Aseptic Processing
- Integration of Risk Management into Quality Systems

30-October 1: Computer Product Supplier Auditing Process Model: Auditor Training
Bethesda, Maryland
www.pdatraining.org/ComputerProduct

The PDA Training and Research Institute is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

For more information on these and other upcoming PDA TRI courses please visit **www.pdatraining.org**

* PDA's *Aseptic Processing Training Program* is not eligible for any discounts.

2010 PDA/FDA Joint Regulatory Meeting

EU Regulator to Stress Framework, Communication

Washington, D.C. • September 13-14 • www.pda.org/pdafda2010

At the *2010 Joint Regulatory PDA/FDA Conference* **Brendan Cuddy** of the European Medicines Agency will give a presentation about the European Medicines Agency perspective on emerging regulations on Monday, September 13. At the same session, **Nakissa Sadrieh** will direct her attention to the U.S. FDA's perspective on upcoming policies, such as the critical path initiative. This project has allowed the FDA to focus resources to stimulate and assist in a national effort to modernize the scientific process through which FDA regulated products are developed, evaluated and manufactured.

Attendees will also learn about the European Medicine Agency's approach it has drafted for the regulatory framework that is being developed to address the regulatory challenges of emerging technologies and novel scientific approaches.

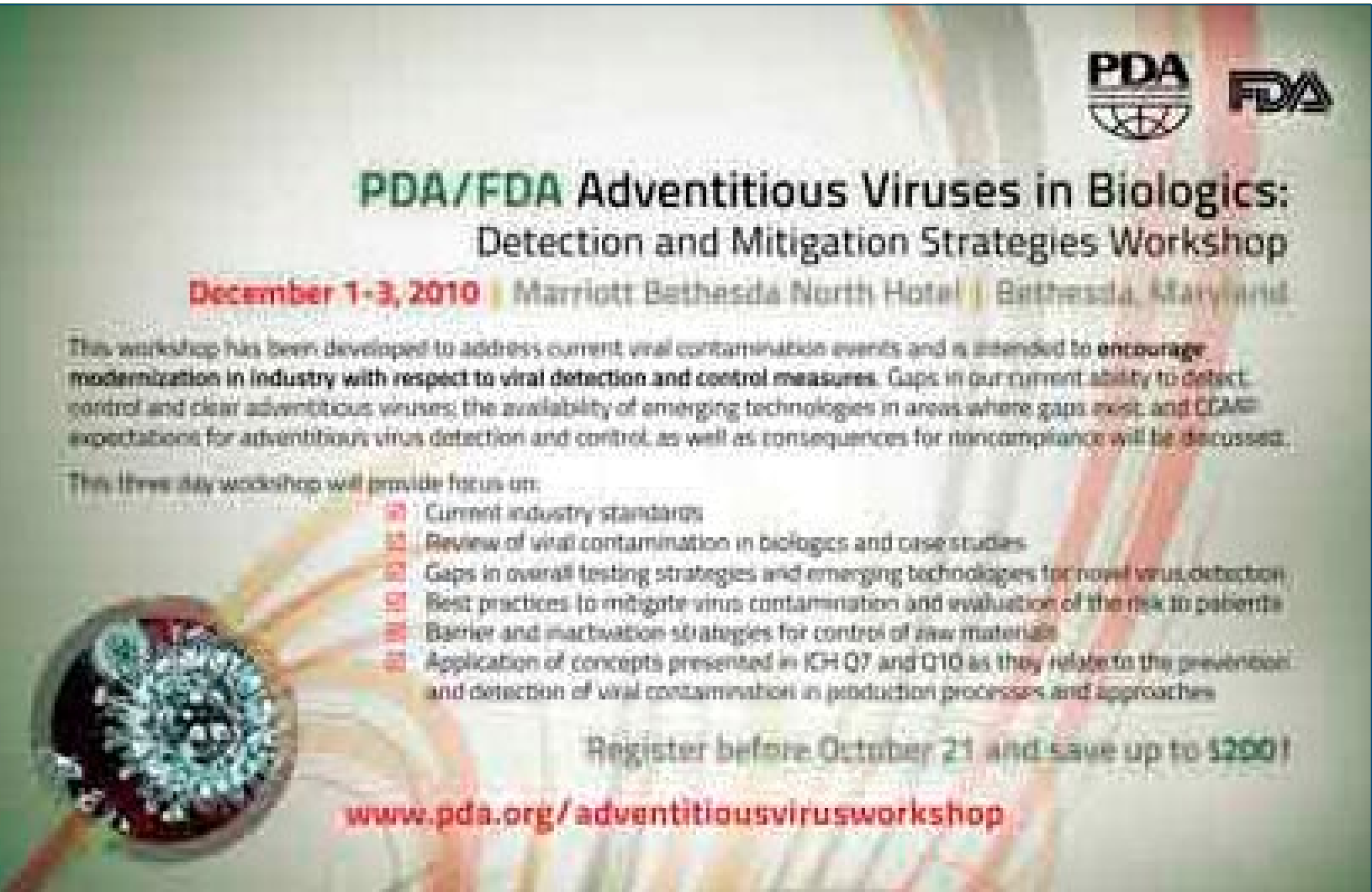
The next day, on September 14, Cuddy will speak about the FDA/EMA/TGA Joint Inspection Program. Cuddy will address the importance of communication between regulators to facilitate harmonized regulatory approaches and how the collaboration between the EU, U.S. FDA and TGA provide a unique opportunity for open dialogue.

The initiated API Inspection Pilot Program will also be spoken about at length. It supports a global supply chain for APIs and puts an increasing demand for international collaboration on inspection work sharing on a risk-based approach. The project also focuses on better use of international inspectional resources which allow for an increase in inspectional coverage outside participating regions and better coordination/collaboration/information sharing between authorities on sites of common interest. This can contribute to risk-based inspection approaches and improve inspection efficiency.

To date, there has been an increase in transparency and visibility of inspection planning, a decrease in "duplicate injections," and an increase in the number of inspections performed that are of value to more than one authority.

At this session, a regulator from the FDA will also concentrate on the benefits and strategy of international collaborations facilitated with the Pharmaceutical Inspection Cooperation Scheme (PIC/s).

Questions will be addressed at both sessions from the regulators.



PDA

2010 PDA Europe Workshop

Lean Manufacturing

Gaining a Competitive Advantage

21-22 September 2010, Dublin/Ireland

Workshop, Exhibition

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www.pda.org/LeanMan2010

Today Lean manufacturing is a key to competitiveness in industry. The Lean manufacturing approach has emerged from the paradigm of Japanese car manufacturing. It aims to increase value for the end customer and to reduce waste by continuous process improvements. Such processes are facilitated by approaches and tools like Lean Thinking and Six Sigma. Also for pharmaceutical and biotech companies Lean manufacturing is a competitive advantage. That is why Lean processes have to be implemented. Nevertheless in such a strongly regulated environment drug safety, quality and regulatory requirements have to be met while changing to and applying lean processes. The program of this two-day workshop will comprise a comprehensive introduction to lean approaches, tools and its application to pharmaceutical and biotech production. The value of Lean to pharmaceutical production will be explained by Experts from industry. They will present successful examples, point-out challenges and identify pitfalls in changing to Lean manufacturing. Regulatory support, requirements and inspection issues of lean processes will be outlined by experts from regulatory authorities, focusing on ICH guidelines Q8, Q9, Q10 and EU variations. The current best practice of Lean drug manufacturing will be illustrated by a biotech case study and a pharmaceutical case study from Ireland. Poster session, networking activities and pauses will provide additional time to deepen your knowledge, discuss with experts and network. Join our workshop and learn from the experts how Lean can be implemented into your production environment and how it will be a competitive advantage for your company.

The Parenteral Drug Association presents...

2010 PDA/FDA Joint Regulatory Conference

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1. Opening Keynote Address by **Margaret Hamburg**, MD, Commissioner of Food and Drug Administration
2. Over 30 FDA Speakers
3. 40 Sessions to Hear Regulatory and Industry Perspectives
4. Co-sponsored by the FDA

This conference is designed with you in mind and delivers **quality topics and content**.

Margaret Hamburg, MD, Commissioner of Food and Drug Administration is confirmed as the opening keynote speaker for the *2010 PDA/FDA Joint Regulatory Conference*.

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Immediately following the conference is the *PDA Extractables and Leachables Workshop*, focused on the impact and quality of packaging, processing materials and delivery systems.

PDA's Training and Research Institute will offer **seven in depth courses** on September 16.

Register by August 2nd and save up to $200!