People • Science • Regulation

PDA Letter

Volume L • Issue 1 www.pda.org/pdaletter January 2014

COMPOUNDING IN THE UNITED STATES: A RETROSPECTIVE 28

The Parenteral Drug Association presents...

2014 PDA Europe

Modern Biopharmaceutical Manufacturing

Manufacturing of the Future

This year´s conference will particularly address burning topics relevant to a fast changing and highly regulated environment such as Dedicated Facilities, Continuous Processing, Multi-Product-Lines as well as Flexible and Single-Use Factories. Practical approaches to the challenges in development and manufacturing of biopharmaceutically and biotechnologically derived products in the current GMP environment, and Quality by Design perspectives will also be discussed.

The rapidly evolving international environment in which biopharmaceutical industry is working confronts us with new challenges daily. Innovations and new developments offer solutions to some of these challenges.

A host of international experts will share their experiences by presenting the latest practices, methods and Case Studies associated with the industrial development and production of vaccines & biopharmaceuticals. Risk Management concepts applied to these new technologies and innovative operations will be discussed as well.

If you are operating in the biopharmaceutical business, whether in a large or small firm, this annual international survey of current best practices makes for the ideal lead into 2014, and an opportunity to network with opinion leaders and experts in these fields.

There will be plenty of time for questions and discussion, making for a very interactive and fruitful meeting.

We will be pleased to meet you in March 2014, and would also like to take this opportunity to celebrate the 10th anniversary of the French PDA Chapter.

Jean-Luc Clavelin, *Co-Chair, Consultant*
Christophe Grimm, *Co-Chair, Sartorius Stedim Biotech*

25-26 March 2014
Lyon | France

CONFERENCE 25-26 Mar | **EXHIBITION** 25-26 Mar | **TRAINING COURSES** 27-28 Mar

europe.pda.org/Biopharm2014

Volunteer Opportunities at PDA

Leadership

- PDA Executive Officers
- Director
- Scientific Advisory Board
- Biotechnology Advisory Board
- Regulatory Affairs and Quality Advisory Board
- PDA Committee Chair/Co-Chair
- Task Force Co-Chair

- Author/Contributor to the *PDA Letter*
- Author/Contributor to the *PDA Journal*
- Poster Presenter
- Attend Chapter Committee/Planning Meetings
- Technical Report Peer Reviewer

- Speaker
- Chapter Leader
- Task Force Member
- TRI Instructor
- Interest Group Leader

PDA Committees:

- Program Planning Committee
- Membership Committee
- PDA Letter Committee
- Education Committee
- Audit Committee

- PDA Membership
- Attend Global PDA Meetings
- Attend Chapter Events
- Survey Reviewer
- Interest Group Member
- Attend TRI Courses

Getting Involved

1,000 Over 1,000 volunteers worldwide actively carry out PDA's Mission

volunteer@pda.org

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Cover

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2014 Board of Directors

PDA is pleased to announce the results of the 2014 Board of Directors and Officers election.

Executive Committee

Congratulations to **Hal Baseman,** Principal and Chief Operations Officer, ValSource, who assumes the role of PDA Chair for the 2014–2016 cycle.

Martin VanTrieste, Sr. Vice President, Quality, Amgen, has been elected as Chair-Elect.

Rebecca Devine, PhD, Regulatory Consultant, has been elected as Treasurer.

Michael Sadowski, Director, Sterile Manufacture Support, Baxter, was elected to the position of Secretary.

Anders Vinther, PhD, Vice President, Quality Biologics, Genentech, moves into the Immediate Past Chair position for the next two years.

PDA would also like to thank **Maik Jornitz,** Chief Operating Officer, G-Con, for serving as PDA Chair in 2010–2011 and as Immediate Past Chair 2012–2013.

Chair
Hal Baseman
ValSource

Chair-Elect
Martin VanTrieste
Amgen

Secretary
Michael Sadowski
Baxter Healthcare

Treasurer
Rebecca Devine, PhD
Regulatory Consultant

Immediate Past Chair
Anders Vinther
Genentech

Directors

PDA Congratulates and welcomes one new Director to the Board: **Joyce Bloomfield,** Executive Director, Global GMP Systems & Compliance, Merck.

Returning to the Board is **Veronique Davoust,** PharmD, Manager, Global Quality Strategy, Pfizer, who previously served on the board 2008–2010.

Reelected to the Board are **Jette Christensen,** Aseptic Scientific Director, Novo Nordisk, and **Glenn Wright,** Senior Director, Project Management, Eli Lilly.

PDA thanks **Steve Mendivil,** Executive Director, External Affairs, International Quality, Amgen, and **Susan Schniepp,** Vice President, Quality and Regulatory Affairs, Allergy Laboratories, for their service to the Board.

Joyce Bloomfield
Merck

Ursula Busse, PhD
Novartis

Jette Christensen
Novo Nordisk

Veronique Davoust
Pfizer

Ian Elvins
Elvins & Associates

John Finkbohner, PhD
MedImmune

Gabriele Gori
Novartis

Stephan Rönninger, PhD, Amgen

Junko Sasaki
Dainippan Sumitomo Pharma

Lisa Skeens, PhD
Hospira

Christopher Smalley, PhD
Merck

Glenn Wright
Eli Lilly and Company

Membership Survey Winner Announced

We are pleased to congratulate **Joe Vigil** from Genentech whose name was drawn from those who completed the 2013 PDA Membership Survey. He received an Apple iPad courtesy of PDA.

PDA thanks those who completed the survey and encourages members to keep an eye out for future surveys and PDA Pulse questions.

BioPharm International

November 1, 2013

"Challenges in Managing the Cold Chain"
tinyurl.com/oeabsxt

—Susan Haigney

BioProcess International

November 2013

"Effects of Pressure Sensor Calibration Offset on Filter Integrity Test Values"
—Magnus Stering
tinyurl.com/ox4rtck

"Impact of Process Interruption on Virus Retention of Small-Virus Filters"
—Dan LaCasse, Paul Genest, Kara Pizzelli, Patricia Greenhalgh, Lori Mullin, and **Ashley Slocum**
tinyurl.com/pdta7xw

Compliance & Learning for Life Science Companies

December 16, 2013

"Industry Identifies Quality Metrics at PDA Event" **—Rob Sims**
tinyurl.com/ouoporq

IPQ News in Depth

November 1, 2013

"Successful Tech Transfer to a CMO Depends on a Strong Quality Agreement and Open Communication Pathways, FDA Asserts"

November 5, 2013

"Level of Industry Response to FDA's Quality Agreement Draft Guidance Reflects Contracting Challenges; Terminology at Issue"

November 19, 2013

"Transformation in Industry Practice Must Accompany FDA's Generics Program Overhaul to Meet GDUFA Goals, OGD Stresses"

December 3, 2013

"Interactions Between OGD's Inactive Ingredients Database Working Group and IPEC on IID Content and Functionality Bearing Fruit"

December 17, 2013

"Industry is Exploring How to Empower Pharmacovigilance Programs to Find GMP Root Causes"

The Gold Sheet

November 21, 2013

"Are Cleanrooms Clean? Human Microbiome Project Raises Some Questions"
—Bowman Cox

Pharmaceutical Technology

December 2, 2013

"Implementing QbD in Sterile Manufacturing"
—Susan Haigney

tinyurl.com/p3mamgz

Drug Industry Daily

December 9, 2013

"FDA to Consider Quality Metric Rankings at Request of Industry"

December 10, 2013

"Industry Pushes Go-Slow Approach to Quality Metrics Reporting"

Washington Drug Letter

December 16, 2013

"Industry Identifies Top 10 Quality Metrics For FDA's Proposed Monitoring Program"
—Robert King
tinyurl.com/o3szrxg

What's launching March 18?

THE LATEST PHARMACEUTICAL & BIOPHARMACEUTICAL TECHNOLOGY

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See all of these products at INTERPHEX (photos from left to right): EMD Millipore Corp., IMA Life North America Inc., GEA Process Engineering, Inc., Thomas Engineering Inc., Korber Medipak, Biologics Modular

PDA and INTERPHEX Sign Sponsorship Agreement

PDA and the International Pharmaceutical Expo (INTERPHEX) are pleased to announce a three-year sponsorship agreement. PDA will be the premier sponsor of INTERPHEX. This sponsorship aligns the objectives of both organizations to service key needs of the global pharmaceutical and biopharmaceutical industry by driving innovation and advancement.

INTERPHEX is an annual trade event dedicated to the pharmaceutical and biopharmaceutical industry and will be held March 18–20, 2014 at the Jacobs Javits Center in New York City.

"Our sponsorship of INTERPHEX reflects our support of the continued enhancement of industry learning and improvement, areas we find present at INTERPHEX," stated **Richard Johnson,** PDA President. "Nonprofits and corporate entities can work together to leverage best practices, in real-time, to the benefit of our industry. Our collaboration with INTERPHEX is one example of this effort and we are pleased to move forward in this shared endeavor."

PDA will be directly involved in developing the INTERPHEX conference programming identifying speakers from industry and regulatory agencies and developing a PDA sponsored cGMP Track. PDA members will have extensive educational and networking opportunities including an exclusive Association Membership Lounge.

"A long-term sponsorship with PDA, both on national and global levels, aligns us with thought leaders across the globe," stated **Bob Stewart,** Vice President of INTERPHEX. "By fostering alliances with successful non-profit organizations like PDA, we acknowledge our investment in the future of the biopharmaceutical industry, and ultimately deliver unrivaled opportunities for knowledge, interaction, and professional growth."

PDA Volunteer Spotlight

Steve Mendivil

- Executive Director, External Affairs, International Quality
- *Amgen*
- Member Since | 1991
- Current City | Thousand Oaks, California
- Originally From | San Jose, California

I originally had a desire to better understand inspectional trends

Steve worked his way up to a full Ironman triathlon in 2012

What do you hope is the main takeaway for attendees from your talk at the *2013 PDA Pharmaceutical Quality Metrics Conference?*

An understanding of the complexity of metrics, and which are appropriate to share externally to minimize unintended consequences.

Why did you decide to volunteer for PDA?

I originally had a desire to better understand inspectional trends. Overtime, I gradually expressed a desire to join RAQC and eventually had to opportunity to join.

How can volunteers achieve leadership roles at PDA?

By being active participants and fulfilling their commitments.

How has being a PDA member helped your career?

More than I would have imagined. I remember attending my first PDA conference in San Francisco being very confused, and not understanding many of the presentations. I kept attending conferences, reading, and eventually developed a small network, which lead to a job at Genentech. After moving to Amgen, I became more involved in PDA's RAQAB and eventually was nominated to be co-chair under **Zena Kaufman**. My RAQAB experience leading volunteer teams lead to my nomination and election on the Board of Directors. Because of all of these external activities, it became evident that I needed more time to focus on external activities. Luckily my management was supportive and created a new position managing external affairs across Amgen's operations.

Looking back, what is one thing you wish you'd known when you started out in your career?

How important teamwork is rather than trying to find the solution on your own.

What trends in your industry are you most excited about?

I see more focus on adopting quality systems techniques that have been successfully implemented in other industries.

vai

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chapter update

Southern California Chapter Elections

Chapter President John Holmgren, Allergan

I would like to personally welcome the new chapter officers to the Southern California chapter board. Each individual brings vast experience in the pharmaceutical industry and energy to lead the chapter initiatives. Our team which includes a committed group of board volunteers is looking forward to delivering another remarkable year of programs for the members of the Southern California chapter.

PDA Who's Who

Brian Underhill, General Manager/ Principal Biospeq

Bonnie Ward, President and CEO, Quality Compliance Partners

Ruchika Raval, President, Global Biopharm Regulations

Stefany Goldman, Business Development Manager, NSF

Stephanie Powers-Kurtz, Southwest Territory Sales Manager, Veltek

Randy George, Sales/Business Development Director, RJG

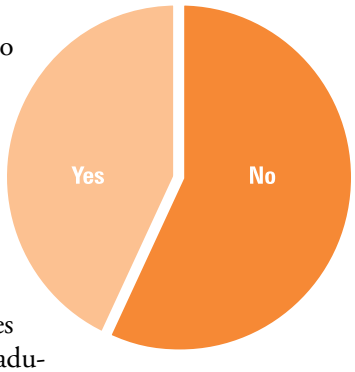
I would also like to extend our appreciation to the outgoing chapter officers: President **Saeed Tafreshi** and Treasurer **Bill Nichols.** Their dedication to PDA and innovated spirit resulted in tremendous programs in the area and built our strong foundation for chapter events for years to come."

The following were elected as officers for PDA's Southern California Chapter in 2014.

- President-Elect: **Brian Underhill**
- Vice President (San Diego area): **Bonnie Ward**
- Vice President (Orange County and Los Angeles area): **Ruchika Raval**
- Secretary/Program Committee Chair: **Stefany Goldman**
- Treasurer: **Stephanie Powers-Kurtz**
- Membership Committee Chair: **Randy George**

PDA Pulse

More than 40% of Companies Plan to Hire Recent Graduates in 2014



Recently, PDA reached out to members involved in hiring to ask if their companies planned to hire recent college graduates in 2014. Nearly 43% said their companies plan to hire recent graduates compared to just over 57% who indicated their companies do not plan to hire recent graduates.

P1: Medical and Regulatory Concerns with Particulate Matter

(l-r) Markus Lankers, PhD, rap.ID Particle Systems; John Ayres, MD, Eli Lilly; John Shabushnig, PhD, Insight Pharma

P3: Packaging Materials

(l-r) Nicholas DeBello, DeBello & Associates; Deborah Shnek, PhD, Amgen; Roy Cherris, Bridge Associates

P5: Transition from Manual to Automated Inspections

(l-r) Markus Lankers, PhD, rap.ID Particle Systems; Daniel Berdovich, Micro Measurement Labs; Daniel Lamarre, Mallinckrodt

P6: Automated Inspections

(l-r) Fernand Koert, Teva; Roy Cherris, Bridge Associates; Mauro Giusti, PhD, Eli Lilly

P8: Panel Discussion

(l-r) John Shabushnig, PhD, Insight Pharma; D. Scott Aldrich, Ultramikro; Deborah Shnek, PhD, Amgen; Fernand Koert, Teva; Nicholas DeBello, DeBello & Associates

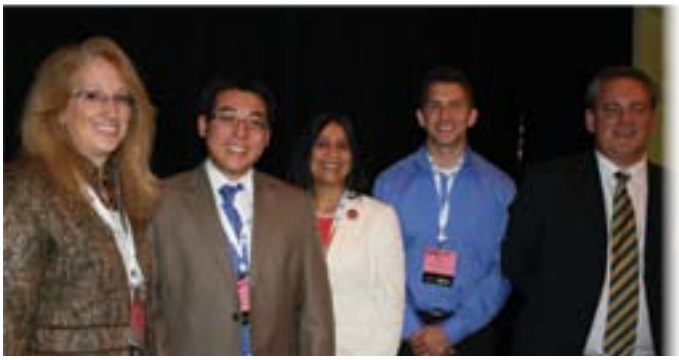
P7: Process Monitoring and Control

(l-r) Roy Cherris, Bridge Associates; Markus Lankers, PhD, rap.ID Particle Systems; John Ayres, MD, Eli Lilly

Attendees had the opportunity to take a guided tour of PDA's TRI facilities during conference down time.

P4: Emerging Leaders

(l-r) Hilary Chan, Shire; Christopher Day, BMS; Heather Greiner, Pfizer; Sam Elrashidy, Bayer; Deborah Gross, Merck



B1: Lean Laboratory Concepts

(l-r) Amy McDaniel, PhD, Pfizer; Strong Huang, bioMerieux; Hemangini Patel, Pfizer; Kevin Walsh, Rapid Micro Biosystems; Gordon Walker, Genentech

A2: Microbiological Quality of Nonsterile Manufacturers

(l-r) Scott Sutton, PhD, Microbiology Network; Tony Cundell, PhD, Consultant; Julie Barlasov, Perrit Laboratories, John Metcalfe, PhD, U.S. FDA

B2: Recent Discoveries with Endotoxin Testing

(l-r) Cheryl Platco, Merck; Karen McCullough, MMI Associates; Carolyn Braithwaite Nelson, Terumo; James Cooper, PharmD, Endotoxin Consulting Services; Jay Bolden, Eli Lilly

P2: Urban Myths

(l-r) Robert Repetto, PhD, Pfizer; Rich Levy, PhD, PDA; Ken Paddock, Baxter

P3:

(l-r) Ian Critchley, PhD, Cerexa; Sam Elrashidy, Bayer

A4: Globalization Challenges

(l-r) Kalavati Suvarna, PhD, U.S. FDA; Miguel Nogueras, PhD, Abbott

P7: Ask the Regulators

(l-r) Marla Stevens-Riley, PhD, U.S. FDA; Patricia Hughes, PhD, U.S. FDA; David Hussong, PhD, U.S. FDA; Ed Balkovic, PhD, Genzyme; Mike Miller, PhD, Microbiology Consultants; Scott Sutton, PhD, Microbiology Network

P1: Needs and Challenges for Using New Technologies

(l-r) Michael Wiebe, Quantum Consulting; Arifa Khan, PhD, U.S. FDA; Philip Krause, MD, U.S. FDA; Laurent Mallet, PhD, Sanofi

P2: Performance Evaluation: Current and New Methods

(l-r) Jens Modrof, PhD, Baxter; Siemon Ng, PhD, Sanofi; Mark Plavsic, Genzyme

P3: Performance Evaluation: Technical Considerations

(l-r) Christopher Wang, Merck; Jean-Pol Cassart, PhD, GSK; Kathryn King, U.S. FDA

P4: Development and Optimization of Data Analysis Pipelines

(l-r) Jean-Pol Cassart, PhD, GSK; John Thompson, PhD, Merck; Robert Charlebois, PhD, Sanofi

P5: Bioinformatics and Databases

(l-r) Laurent Mallet, PhD, Sanofi; Tom Slezak, Lawrence Livermore National Laboratory; Carolyn Wilson, PhD, U.S. FDA

P6: Applications of New Analytical Technologies

(l-r) John Kolman, PhD, BioReliance; Paul Shabram, PaxVax; Marc Eloit, Institut Pasteur; Paul Duncan, PhD, Merck

P8: Experts Panel Discussion

(l-r) J. Rodney Brister, PhD, NIH; Robert Charlebois, PhD, Sanofi; Konstantin Chumakov, PhD, U.S. FDA; Arika Khan, PhD, U.S. FDA; Jens Modrof, PhD, Baxter; Tom Slezak, Lawrence Livermore National Laboratory; Jean-Pol Cassart, PhD, GSK; Paul Duncan, PhD, Merck

P5: Closing Plenary – U.S. FDA CDER Panel Discussion

(l-r) Russell Wesdyk; Rick Friedman; Francis Godwin; Faiad Rahaman; Steven Lynn; Karthik Iyer; Carmelo Rosa; Alex Viehmann; Jason Urban, PhD

P5: Closing Plenary – Panel Discussion

(l-r) Steve Mendivil, Amgen; Janet Woodcock, MD, U.S. FDA; Anders Vinther, PhD, Genentech; Marty Nealey, Hospira; Jason Orloff, PharmStat; Ferdinando Aspesi, Novartis; Barbara Allen, Eli Lilly; Jeff Rope, Sandoz

(l) Interest in the workshop was strong even through the final session which ended at 6 p.m.; (r) Conference co-chair Steve Mendivil speaks with attendees after the conclusion of the meeting.

snapshot

Technical Report Shows Importance of Extemporaneous Preparation of Clinical Trial Materials

Jahanvi (Janie) Miller, PDA

Even though cGMP isn't strictly enforced in clinical trial material manufacturing environments, appropriate controls must be in place to ensure patient safety. *Technical Report No. 63: Quality Requirements for the Extemporaneous Preparation of Clinical Trial Materials* does that in describing the development of quality systems to support this type of preparation without compromise to the clinical trial materials, ensuring product quality and patient safety.

The technical report team concluded that extemporaneous preparation (EP) techniques are widely utilized to prepare an assortment of formulations for various dosage forms in nonconventional preparation sites and nonmanufacturing environments. EP as defined in Technical Report No. 63 is "a type of compounding whereby a drug or combination of drugs and/or excipients is prepared under the supervision of a pharmacist to create a customized medication dosage form in accordance with a clinical protocol."

Since there is not a lot of guidance for EP, the team focused on the current global regulatory environments. Therefore the primary scope of the technical report is to provide recommendations to maintain quality requirements when preparing small-scale clinical trial materials (CTMs) using EP for in-clinic dosing. This report is not to be used for large-scale studies which involve multiple doses and a large quantity of patients. It's also critical for sponsors to comply with all local regulations in place as guidelines will vary depending on location of preparation site. This is why site selection and qualification is an important evaluation done prior to performing any EP activities.

Extemporaneous preparations can also be considered as safety assessment tools, which may be useful to achieve exposure levels greater than would be possible with traditional solid oral dosage forms. As the regulators move closer to a resolution of governing compounding pharmacies and safety concerns with compounding, this technical report serves as a general best practices guide to those developing early phase CTMs. The quality system and documentation practices discussed in this technical report further support patient safety and product quality.

In *Print*

The Limitations Of The Sterility Test

Tim Sandle, PhD, BPL

The following is excerpted from the chapter "Evaluating the Sterility Test" from the PDA/DHI book Sterility Testing *by* ***Tim Sandle,*** *PhD.*

The main part of this chapter considers the limitations of the sterility test on the basis of statistical issues relating to sampling and the scientific arguments relating to the likely recovery, or otherwise, for microorganisms.

The Statistical Limitations of Sampling for the Sterility Test

For aseptically filled products, as well as for many terminally filled products, the sterility test is a mandatory product release test. It is, however, statistically poor at detecting anything other than gross contamination (this limitation has been addressed in a number of studies, for example, Téllez et al., 2006). This limitation relates to the few numbers of articles tested (Brown and Gilbert, 1977). For batches in excess of 500 filled containers, the pharmacopeia only require that 20 samples are included in the sterility test set. This sample size appears to have been set arbitrarily, and it does not provide a statistically significant population with which to estimate sterility (Knudsen, 1949).Although it is unclear how this sample size was derived, the number is grounded, in part, through the sterility test being a destructive test (each article tested via the sterility test is not available for the patient) and therefore to maximize the availability of the batch by using as few units as possible. It remains, nonetheless, that the sample size of 20 provides no confidence that the sterility of a batch of pharmaceutical items has not been compromised.

In relation to sampling, limitations not only apply to the low number of samples tested, but also to the difficulties in selecting asample representative of all significant events during batch filling (Ernst et al., 1969). This is important because contamination

Tech *Trends*

Gamma Sterilization of Pharmaceuticals

Fatima Hasanain, Nordion

The feasibility of gamma sterilization of pharmaceuticals depends on several factors including, but not limited to, the formulation and stability of the pharmaceutical, radiation dose necessary to attain sterility, product packaging and irradiation conditions. Terminal sterilization is preferred where possible to provide patient safety. Typically, a sterility assurance level of SAL of 10^{-6}, where achievable, is prescribed for any devices or substances which will come into contact with compromised human tissue unless a risk assessment can be performed to justify a higher SAL. A sterilization dose of 25 kGy has traditionally been regarded as adequate to treat products with high presterilization bioburden (up to 1000 CFU/product unit). As most pharmaceuticals manufactured in clean environments have low bioburden, a sterilization dose of 25 kGy may lead to overprocessing of the products. When sterilizing a pharmaceutical product, it is critical to optimize the sterilization method to balance the level of sterility assurance without negatively impacting the product.

At the *PDA 8th Annual Global Conference on Pharmaceutical Microbiology*, I presented a poster titled "Gamma Sterilization of Pharmaceuticals – A Review of the Irradiation of Excipients, Active Pharmaceutical Ingredients and Final Drug Product

Continued at top on page 21

Task Force *Corner*

Task Force Reconvenes to Tackle New Therapies

Josh Eaton, PDA

Gene and cell-based therapies (GCBTs) represent a change of paradigm for 21st century healthcare. While the basic science of manipulating genes and cells for use in pharmaceutical products has been around for about 40 years, significant advances have been made during the last 20 years. These types of pharmaceutical products have a strong science base, but to fully progress into the therapeutic arena, they will require careful development, and close interaction between producers and regulators.

Among the issues associated with GCBTs are the need to address the manufacturing challenges and issues related to phase appropriate implementation of GMPs, process adaptation to commercial production, if, when, and how to transition from manual to bioreactor production, and the inherent variability of the end product. These factors and more contribute to the difficulty of defining a control strategy that can ensure the safety and efficacy of the therapeutic.

To further the advancement of quality GCBTs, PDA's Gene and Cell-Based Therapies task force has reconvened following two successful *Advanced Therapy Medicinal Products* (ATMP) conferences in 2012 and 2013. The task force met at the 2013 conference in Florence, Italy to discuss the daunting task of pro-

Continued at bottom on page 21

is unlikely to be uniformly distributed throughout the batch, and thus random sampling cannot detect contamination with absolute certainty. This is of particular importance with aseptic filling where batch specific events can occur. It is possible that certain events can be captured, such as interventions into the aseptic core, where the vials exposed at the time of the activity can be incorporated into the sterility test set (notwithstanding that all events cannot be captured in this way).

The difficulty in detecting a low level of contamination from a batch of filled product can be illustrated by way of an example. To illustrate this an equation is required (equations 1 and 2 below are adapted from Brown and Gilbert, 1977). Consider that p refers to the proportion of contaminated containers in a batch, and q the proportion of corresponding noncontaminated containers. Arranging these, we have two possible expressions:

$$p + q = 1$$

or,

$$q = 1 - p$$

Example 1: Selecting specific contaminated containers from a batch

To take an example where we assume that we have a specific batch where 10% of the containers are contaminated. From this batch, two items are withdrawn.

On this basis, the probability of a single item taken at random showing contamination can be given by the following expression:

$$p = 0.1 \text{ [i.e., 10\% = 0.1]}$$

The probability of such an item being non-contaminated is can be represented by the following expression:

$$q = 1 - p = 1 - 0.1 = 0.9$$

The probability status of the two contaminated articles being detectedmay be expressed in three different forms. These are when:

- both items are contaminated:
  $p^2 = 0.01$
- both items are non-contaminated:
  $q^2 = (1 - p)^2 = (0.9)2 = 0.81$
  and
- one item is contaminated and the other one is noncontaminated:
  $1 - (p^2 + q^2)$
  or
  $1 - (0.01 + 0.81) = 1 - (0.82)$
  or
  0.18 i.e., $= 2pq$

Example 2: Chance of passing a sterility test where contamination is present in a batch

This premise can be expanded further. To take a particular sterility test, with a sample size of n containers, the ensuing probability p of duly accomplishing n consecutive pass results is represented by the following expression:

$$q^n = (1 - p)^n$$

To look at this another way, inmathematical terms, if n is the number of containers tested, and p is the proportion of contaminated containers, and q is the proportion of non-contaminated containers, then:

$$p + q = 1$$

From this it follows that:

$$\text{the probability of rejection} = 1 - (1 - p)^n$$

For example, the pharmacopoeia test for sterility produces a pass result for batches from which 20 items have been tested and shown to be sterile under the conditions of the test. If the proportion of non-sterile items in a batch were to be one in 100, the expression above would be solvable as follows (Halls, 1994):

$$(1 - p) = 0.99$$

Take the logarithm of 0.99

$$\text{Log}_{10}\ 0.99 = -0.0044$$

Solve for $(1 - p)^n$ by multiplication

$$(1 - p)n = (-0.0044) \times 20 = (-0.088)$$

Withdraw from logarithmic form by taking the anti-log

$$\text{Anti-log of } (-0.088) = 0.817$$

Therefore we can show mathematically that with an incidence of one non-sterile item in 100, there is greater than 80% chance of passing the test for sterility.

A follow-on concern, based on the uncertainty of detecting contamination, is that if a batch was to fail the sterility test (due to low level contamination), and the batch was then subject to a repeat sterility test (which is a controversial area discussed later in this book), there is a reasonable chance that it would pass on the second occasion.

In mathematical terms, the probability of passing a batch with some contaminated containers on a retest is:

$$(1 - p)\ [2 - (1 - p)^n]$$

For example, if there is a sample size of 10 and the contamination rate is 5%, then if the sterility test is repeated with another sample size of 10 units the probability of including a contaminated item is again 0.4. However, the probability of both tests being positive reduces as it becomes $0.4 \times 0.4 = 0.16$, which is lower than the probability of the first test, and hence in 84 of 100 such tests the batch will be accepted as sterile.

Example 3: Further cases examining the difficulty of detecting non-sterility in a batch

To illustrate this concept further, the ensuing values for various levels of p (proportion of contaminated containers present in a batch) having essentially a constant sample size are as provided in **Table 11.1** below.

Table 11.1 Table showing the probability of detecting contamination in the sterility test based on different levels of contamination and for different sample sizes

Percentage of Items contaminated	0.1	1.0	2.0	5.0
Sample size 10	0.01	0.09	0.18	0.40
Sample size 20	0.02	0.18	0.33	0.65
Sample size 50	0.05	0.39	0.64	0.92
Sample size 100	0.09	0.63	0.87	0.99

The table values are probabilities (in this, the probability of contamination). Probabilities are given a value between 0 (0% chance or will not happen) and 1 (100% chance or will happen) (Feller, 1968). Therefore, a probability of 0.4 means that on four out of every 10 occasions it is likely that an event will occur (in this context, if a sterility test was conducted 10 times, on four occasions the test would detect contamination and on six occasions it would not detect contamination). These concepts of probability are displayed in Table 11.1.

The outcomes expressed in the table illustrate that the sterility test fails to detect low levels of contamination. The assumption with the table is that it is unknown where in a batch of product the contaminating articles are located (which is often a reasonable assumption).

If different sample sizes are taken (based upon $(1 - p)n$ factor), the table also illustrates that the sample size enhances the probability of detection (interestingly the Australian TGA required a sample size of 30 items in its Test for Sterility until the 1990s. This was the only regulatory agency ever to set a sample size above 20 units). However, the sensitivity of detection only becomes meaningful where a relatively high proportion of the items are contamination (≥5%) and where relatively large sample sizes are taken (≥50). To take an example, outlined in the Australian TGA guideline, with a sample size of 10 and a contamination rate of 5% the probability of including a contaminated item is 0.4 (TGA, 2006). In reality, where contamination does occur, this is normally tied to specific events during batch filling and this would be, in all probability, less than 0.1% of the batch. With the recommended sterility test size required by the pharmacopeia of 20 items, then the relative insensitivity of the sterility test can be quite considerable.

Tech Trends continued from page 19

Formulations." The poster presentation was based on a literature review (to be published in the *PDA Journal of Pharmaceutical Science and Technology*) of more than 100 peer reviewed papers and publications. A summary of findings illustrated that formulation changes, such as addition of radioprotectants or varying the irradiation conditions (temperature, product state, oxygen environment, dose and dose rate) can extend the applicability of gamma irradiation to the terminal sterilization of pharmaceuticals. Many methods are also available to characterize product acceptability for gamma irradiation and the sterilization modality should be carefully evaluated at an early stage in the drug development process. A standardized framework of investigations will aid in identifying candidates for gamma sterilization and streamline the process. Based on regulatory guidelines and published best practices, this presentation has included a decision tree for implementation of gamma irradiation for pharmaceutical products. The review therefore provides a useful reference to the application and versatility of gamma irradiation for pharmaceutical sterilization.

Considering the increasing emphasis on product safety, in combination with the general simplicity of the gamma irradiation approach and its high level of sterility assurance, we expect the application of this technology for pharmaceutical products will continue to grow in the future.

About the Author

Fatima Hasanain, is a Polymer Materials Specialist for Nordion (Canada) Inc. She has varying areas of expertise in radiation effects on polymer materials and gamma sterilization. She is the Technical Manager of the Dosimetry lab at Nordion.

Task Force Corner continued from page 19

viding best practice guidance in the growing field of GCBTs. Led by **Michele Myers,** PhD, of GlaxoSmithKline and **Valerie Pimpaneau** of Voisin Consulting, the team has refocused to address the topic of autologous cell-based therapies and the design of manufacturing control strategies. This will be the first in a series of technical reports tackling these complex and quickly evolving products and their associated production, quality, and safety concerns. The team has an internationally based membership in order to foster a harmonized vision of the GCBT area and includes members of some European regulatory agencies.

If you'd like to join this task force, please contact PDA's **Josh Eaton** at eaton@pda.org.

[Editor's Note: For an overview of the June ATMP conference, please see p. 28 of the November/December *PDA Letter*.**]**

LER Concerns Create Debate Between Industry, Regulators

Rebecca Stauffer, PDA

Lately, there has been a new term abuzz within the pharmaceutical microbiology community: Low Endotoxin Recovery (LER). While the potential threat of endotoxin contamination is well known, the dangers of LER to patient safety, if any, are not as well understood. Unsurprisingly, the topic of LER has engendered debate among microbiologists.

At the Microbiology/Environmental Monitoring Interest Group meeting held during the *PDA 8th Annual Global Conference on Pharmaceutical Microbiology* in October, **Joseph Chen,** PhD, Sr. Principal Scientist, Genentech, offered his perspective on LER based on experience researching the phenomenon.

Chen characterized LER as a masking effect noticed during quantification of endotoxins by LAL testing of biologics. These types of biologic products share common formulation ingredients: polysorbate and citrate or polysorbate and phosphate.

"The masking effect of the endotoxin regarding the LAL testing is not something new," he said. Linking a rapid endotoxin masking of the LAL testing to the common biologic product formulation ingredients, however, is novel to the industry.

Since endotoxins impact patient safety, Chen said that understanding and learning how to manage this masking effect is vital. This is a challenge since there is little regulatory or pharmacopoeial guidance on the phenomenon.

"That's because there's no regulatory requirement of assessing endotoxin stability in the sample," he said, referring to current sampling methods which only require spiking CSE or RSE to a diluted sample at noninterfering concentration (NIC), achieving 50-200% recovery. According to Chen, this approach fails to recognize that potential endotoxin masking due to LER could be present in undiluted product samples while being stored.

He then discussed how LER was first recognized in a Roche laboratory during a quality control study of sampling container change; the LER findings were submitted to all major health authorities over a year ago. Here, the company noticed a spike of CSE to a product in both glass and polyethylene containers that was monitored for seven days' duration. This spike quickly became undetectable, despite all sample controls meeting the acceptance criteria.

"I want to emphasize this is a QC/analytical issue. Indeed, we actually have very, very stringent microbial control in our process and we believe that although our product exhibited this masking effect, there's no or little risk to our products because there's no history of any pyrogenic responses before to our products due to LER," Chen stressed.

Following the investigation into the phenomenon, Chen's team developed the hypothesis that in the presence of chelating salt agents and polysorbates, endotoxins can form a LER complex that is not recognized by the LPS binding receptor on the Factor C. Upon dilution, heating, dispersing agents and adding divalent ions fail to reverse the LER effect.

"We know that the problem happens at the binding of endotoxin to the Factor C step," he said. Further, "the endotoxin is no longer recognizable by the LPS binding receptor of the Factor C, therefore, no activated Factor C to trigger the enzymatic cascade."

Chen's team then communicated their findings to the U.S. FDA in early 2012. The Agency referenced their study data and then issued the pyrogen and endotoxins Q&A guidance in June 2012 for industry ***(1).*** This guidance states that firms should establish procedures for storing and handling samples used for bacterial endotoxin analysis according to laboratory data to demonstrate the stability of assayable endotoxin content. Chen believes that following this guidance will reveal the LER effect, if present, in the products in question. But using the U.S. Pharmacopoeia's LAL methods as written today will not, he maintained.

Next, Chen addressed the issue of hold times.

"It is important to conduct LER and a sample hold time assessment separately with a different set of parameters such as storage duration," he indicated.

A question came up from a health authority regarding the establishment of a maximum final hold time for testing of a final container of drug product using the LAL method. The hold time must be supported by the LER study data. This question came up during a recent biologic product submission.

"Our approach to addressing this question is, No. 1, you have to address the LER and hold time study separately," Chen reiterated. "LER, again, is a very fast, rapid reaction, and usually happens within hours and up to 3 days, so, if you design a LER assessment with a 7-day duration, that's more than enough to capture whether your biologic product formulation exhibits LER."

Ultimately, if a drug product exhibits LER, Chen said there is no value to determining the sample hold time. For products not impacted by LER, however, the sample hold time is a new regulatory expectation. In the end, parameters for sample hold times vary from product to product and the 7-day LER study parameter should not be used to set the maximum hold time.

"For the hold time definitely use a wide range of durations," he said.

Chen then delved into how to accurately address the LER phenomenon using a defined natural endotoxin, recognizing that naturally occurring endotoxins (NOE) was a topic discussed throughout the conference. He explained that his team is working with scientists at Charles River Laboratories "to really look into can we do the same thing for natu-

ral endotoxins as now we have a reference standard of endotoxins (RSE) controlled by USP. Can we find a way for industry and regulatory agencies to agree on how the natural endotoxins should be prepared and standardized by a reputable organization such as USP for LER and hold time assessments? There's no perfect world but at least we believe that the natural endotoxin is more representative of our daily contamination issue. In our recent finding, the defined natural endotoxins did slow down the LER reaction but [this is] not a mitigation."

He further suggested that industry and regulatory bodies work together to define the natural endotoxin preparation step and ascertain how to quantify it. In an effort to resolve these issues, his team selected a water isolate *Enterobacter cloacae*—a common contaminant in pharmaceutical water system, and mimic the natural growth conditions in the environment to purify the natural endotoxins from this organism.

"We actually used the defined natural endotoxin in storage for LER assessment," Chen said, "And looked at its stability as well. The natural endotoxin potency correlated very well to RSE using both kinetic LAL methods."

Additionally, he was "very pleased to see that the linearity correlation of *E. cloacae* natural endotoxins with five different concentrations is almost identical to the performance of RSE," presenting a possibility for a standardized approach for industry. His team, however, continued to pursue alternative methods for resolving the LER issue and is working with the FDA and other health authorities to offer advice to industry. In all his talks with industry he recommends that companies test for potential LER in their biologic products and that this issue shows a need to always control low bioburden levels during the manufacturing of biologics.

"To us, I don't think LER is only our problem at Roche/Genentech," Chen emphasized. "This is really a common threat to the entire industry. Therefore, we are willing to share what we learned with industry. I believe we can only solve this LER problem as a whole."

During the Q&A session following his talk, some members of the audience expressed unease with his findings, and one noted that he felt LER presented little risk to products and instead the focus should be on identifying what the mechanism is, such as specifically identifying those products that would be susceptible to the LER phenomenon.

Chen responded that his team found LER in approximately 60% of their biological products. Thus, he believes LER is a common threat to the biotech industry.

Another audience member, a regulator with FDA, pointed out that the Agency is seeing this problem at some companies but not others and "we really don't understand enough about it and I think we need to find out to what extent this

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2014 PDA UPCOMING EVENTS

JANUARY EVENTS

22-24
Environmental Mycology Identification Workshop
Bethesda, Maryland
www.pda.org/mycology

28-29
Joint Regulators/Industry QbD Workshop
London, United Kingdom
https://europe.pda.org/EMA2014

FEBRUARY EVENTS

3-7
2014 Aseptic Processing Training Program – Session 1 Week 1
(Week 2: March 3-7)
Bethesda, Maryland
www.pda.org/2014aseptic1

17
Pre-Conference Workshop on Bacterial and Endotoxin Testing
Berlin, Germany
https://europe.pda.org/PWSBACT2014

18-19
Pharmaceutical Microbiology
Berlin, Germany
https://europe.pda.org/Microbio2014

20
Microbial Contamination Control in the Pharmaceutical Industry
Berlin, Germany
https://europe.pda.org/Contamin2014

20-21
Rapid Microbiological Methods & An Overview of the New Technical Report 33
Berlin, Germany
https://europe.pda.org/TCRMM2014

20-21
The A to Zs of Biofilm Control, Monitoring, Validation, and Excursion Investigations of Pharmaceutical Water Systems
Berlin, Germany
https://europe.pda.org/Biofilm2014

20-21
An Introduction to Visual Inspection – Session 1
Bethesda, Maryland
www.pda.org/visual1

www.pda.org

For an updated PDA calendar of events please visit
www.pda.org/calendar

Save these dates!

MARCH EVENTS

10
Pre-Conference Workshop on Elastomeric Closures
Brussels, Belgium
https://europe.pda.org/PWSElasto2014

11-14
Parenteral Packaging
Brussels, Belgium
https://europe.pda.org/ParPack2014

13
Container Closure Integrity – Regulations, Theory, Test Methods, Application
Brussels, Belgium
https://europe.pda.org/ContainerInteg2014

13
Interest Group Meeting Pre-filled Syringes
Brussels, Belgium
https://europe.pda.org/IGPrefilled2014

13
Identification and Classification of Glass Defects – PDA Technical Report 43
Brussels, Belgium
https://europe.pda.org/TR432014

13-14
Post-Conference Workshop on Extractables & Leachables
Brussels, Belgium
https://europe.pda.org/WSE&L2014

14
Container Closure Systems
Brussels, Belgium
https://europe.pda.org/CCS2014

17-21
Fundamentals of Aseptic Processing – Session 1
Bethesda, Maryland
www.pda.org/apfundamentals1

18-19
PDA/PICs API Training Course
Johannesburg, South Africa
https://europe.pda.org/API2014

18-20
2014 Interphex – PDA Premier Sponsor
New York, New York

25-26
Modern Biopharmaceutical Manufacturing
Lyon, France
https://europe.pda.org/Biopharm2014

27
Technical Transfer
Lyon, France
https://europe.pda.org/TechTrans2014

27-28
Environmental Monitoring
Lyon, France
https://europe.pda.org/Environ2014

March 31–April 9
2014 Aseptic Processing Training Program – Session 2 Week 1
(Week 2: May 5-9)
Bethesda, Maryland
www.pda.org/2014aseptic2

Get a Handle on Knowledge Management

Joseph Horvath, PhD, Takeda Pharmaceuticals, and Program Committee Member

***2014 PDA Knowledge Management Workshop* • Bethesda, Md. • May 19–22 • www.pda.org/KM2014**

Can your company efficiently mine prior knowledge to accelerate early process development? Can it bring insight gained in process characterization rapidly to bear when investigating a problem in commercial manufacturing? Can it locate and make sense of reports, analyses, and source data associated with acquired or legacy products when the authors of those reports have since transitioned out of the company?

If you answered "yes" to all of these questions, then your company is likely in the vanguard of knowledge management—the systematic acquisition, analysis, storage and dissemination of information and knowledge about products, manufacturing processes and components. But if you answered "sometimes" or "sort of" to these questions, your company is likely wrestling with how to go about improving in this area. This is where most companies find themselves today.

Knowledge management is a key enabler of the new paradigm that has been outlined by the ICH and health authorities' expectations in this area are evolving. Unfortunately, although experience with knowledge management is accumulating rapidly in some companies, there is little in the way of either established best practices or the common terminology and frameworks needed to promote their development. It is for these reasons that PDA and our program committee will be bringing together professionals with experience and interest in knowledge management for a two-day workshop in May 2014.

The workshop will be an opportunity for dialogue and sharing of experiences between bio/pharmaceutical companies, health authority representatives, and leading knowledge-management practitioners from other industries. The program of presentations, working sessions, and working session "readouts" has been designed to promote interaction and to begin to establish a foundation of practical knowledge that participants can put to use in their own companies.

The agenda and confirmed presenters for the workshop have now been posted on the PDA website. On behalf of the program committee, I encourage you to review these materials and join us in Bethesda, Md. this May.

Explore Cutting Edge Science this April

Hal Baseman, ValSource

The Annual Meeting is PDA's most comprehensive science and technology-focused gathering. The theme, "Biopharmaceutical and Sterile Manufacturing – Embracing Innovation to Meet Global Challenges," has been carefully chosen and worded. It reflects the need for industry to meet the issues and demands of a changing technical, regulatory, and business climate. It represents an opportunity for attendees to not only become aware of what's happening in the industry, but to solve issues.

The opening keynote speakers will set the tone, reinforcing the day to day aspects of our jobs with the overall objective—providing safe and effective products to patients. The ending key note speakers will encourage attendees to think to future challenges and solutions. In between, plenary and session speakers will present the latest in science and innovation. To that end, the individual session tracks will present detailed discussions on how to meet challenges related to biological science, sterile product manufacturing, innovative technology, process validation, quality systems, outsourcing, investigational techniques and aging facilities.

In addition to the individual sessions, 14 technical and regulatory-focused Interest Group meetings will be held during the *2014 PDA Annual Meeting*. Interest groups represent a less formal venue, to exchange of knowledge in an environment which allows you to have a voice.

It is also important to note that two significant events will take place at the end of the Annual Meeting. If you are responsible for biologic product sterility assurance, you will want to attend a the postconference workshop on bioburden and biofilm. The workshop will include speakers and content from the upcoming technical report on the topic.

And if you want even more detailed knowledge on topics presented at the Annual Meeting, please consider attending one of the many PDA TRI courses in San Antonio, Texas. The courses will cover risk-based product development for combination products, biosimilars, quality risk management of biotechnology product, process validation, moist heat sterilization, and quality assurance/control for cell-based therapeutic products.

2014 PDA Annual Meeting • San Antonio, Texas • April 7–11 • www.pdaannualmeeting.org

On a final note, perhaps the most valuable aspects of the Annual Meeting are the networking opportunities, which give attendees the opportunity to enter open discussion and share viewpoints with colleagues, industry experts and regulators. Attendees will come away informed and knowledgeable, with answers, and with a better sense of how to meet the challenges facing drug product manufacturing.

The success of the Annual Meeting is dependent on your participation and engagement. So, I want to personally invite you to attend what will be a remarkable event. If you do, then I can assure you and we will find the experience rewarding.

LER Concerns Create Debate Between Industry, Regulators continued from page 22

is a problem and what to do about it."

In the end, Chen emphasized that he feels industry can address any potential issues resulting from LER by developing harmonized processes across the board.

"It's not a perfect world but, again, we need to standardize the LER assessment. We need a standardized approach to assess LER to ensure the LAL methods are suitable for our release tests," he said. "I am wondering why there are different LER results from other companies even with LER causing formulation ingredients in their biologic products. Anybody can make their study parameters different which can lead to different results, so why not just try to standardize it?"

Reference

1. Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers, U.S. Food and Drug Administration: June 2012 www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm314718.htm

About the Expert

Joseph Chen currently holds the Sr. Principal Scientist title and oversees microbiology operations at Roche/Genentech for the Biologic Quality Control Network. He did his graduate studies at UCSF with Dr. Jack Levin, one of the founders of LAL gel-clot method.

COMPOUNDING IN THE UNITED STATES: A RETROSPECTIVE

Eric Kastango, Clinical IQ

COMPOUNDING is the art and science of preparing medications for an individual patient either by a pharmacist or under the supervision of a pharmacist, pursuant to an order from a licensed prescriber. The compounding pharmacist can combine individual ingredients in the exact strength and dosage form to meet a patient's specific needs. This can be necessary if commercially available medication is inappropriate for a specific patient due to clinical reasons, such as allergies to dyes or other ingredients, or due to population factors, including newborns, children and the elderly. Sometimes the

medication may be compounded due to a shortage of manufactured product.

Compounding has its origins with the beginning of the pharmacy profession itself. At one time, nearly all prescriptions were compounded. But the advent of mass drug manufacturing in the 1950s and '60s led to compounding's rapid decline. The pharmacist's role as a preparer of medications quickly changed to that of a dispenser of manufactured dosage forms, and most pharmacists were no longer trained to compound medications. Today, a pharmacist's role includes more clinical and direct patient care services, such as administering vaccinations, managing anticoagulation clinics and participating in stewardship programs designed to ensure proper use of antibiotics. Today, only one in six pharmacy graduates is prepared for sterile compounding work ***(1).***

Fourteen months after the worst pharmacy compounding-related tragedy to date, at the New England Compounding Center in Massachusetts, we are only marginally closer to having a safer system. As of Oct. 23, 2013, allegedly 751 patients were adversely affected by three lots of contaminated methylprednisolone acetate suspension injectable compounded at NECC and 64 are dead ***(2).*** In addition to fungal meningitis, patients who received medications from this pharmacy have also reportedly experienced paraspinal, spinal and peripheral joint infections. Catastrophic patient care events involving pharmacy-prepared sterile product preparations have occurred since the 1970s, and the Institute for Safe Medication Practices has compiled a list of selected compounding incidents occurring since the 1990s ***(3).***

Article at a Glance

- Recommendations for compounding first developed in the 1980s
- Regulators first attempt at regulating compounding led to 503A
- Drug Quality and Security Act reinstates 1997 503A language

Groups, Laws Earlier Sought to Address Compounding

One of the first groups to address this issue was the National Coordinating Committee on Large Volume Parenterals. This body developed and recommended standards of practice for the preparation, labeling and quality assurance activities of hospital pharmacy admixture services, completing its objectives in the 1980s. Since that time, the pharmacy profession and its professional organizations and associations continue to struggle to develop and adopt uniform standards of practice in this area. In the early '90s, different pharmacy-related organizations (American Society of Health-System Pharmacists, U.S. Pharmacopeia and National Association of Boards of Pharmacy) published recommendations in an effort to provide advice to pharmacists and technicians responsible for preparing sterile products. A consistent theme from these recommendations was that the compounding pharmacist was responsible for ensuring that sterile preparations were prepared, labeled, controlled, stored, dispensed and delivered properly. The ultimate goal was to ensure the quality and integrity of pharmacy-prepared sterile products. None of these recommendations were uniformly adopted or accepted.

Also during the '90s, U.S. FDA regulators began to scrutinize compounding pharmacies more closely as the number of facilities grew. The FDA was seeing more pharmacies conducting business out of their scope of practice and acting like manufacturers, compounding medications in quantities in excess of prescriptions. In 1992, the Agency issued a Compliance Policy Guide on pharmacy compounding. This guidance document was used to determine if the compounding activities of a pharmacy met the federal exemptions for regulation as a registered entity. **David Kessler,** MD, then FDA commissioner, warned members of Congress in 1996 that drug compounding pharmacies would spawn a "shadow industry" of unapproved drugs, possibly resulting "in serious adverse effects, including death" ***(4).***

The FDA Modernization Act of 1997 included an amendment to the 1938 Federal Food, Drug and Cosmetic Act by adding section 503A (21 U.S.C. 353a), which governs the application of federal law to pharmacy compounding. Under section 503A(a) of the Act, a compounded drug product is a drug product made in response to, or in anticipation of, receipt of a valid prescription order or a notation on a valid prescription order from a licensed practitioner that states the compounded product is necessary for the identified patient. Compounding does not include mixing, reconstituting or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling.

Per section 503A, compounded drug products are exempt, under certain circumstances, from three key provisions of the act:

1. the adulteration provision of section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B) (concerning cGMP requirements)
2. the misbranding provision of section 502(f)(1) (21 U.S.C. 352(f)(1) (concerning the labeling of drugs with adequate directions for use)
3. the new drug provision of section 505 (21 U.S.C. 355) (concerning the use of drugs under INDs and the approval of drugs under NDAs or ANDAs)

Concurrent to these regulatory and legal proceedings, a couple of compliance surveys were conducted by the American Society of Health-System Pharmacists showing poor compliance to their voluntary sterile compounding quality systems and series of events involving patient harm and death from improperly compounded medications. The lack of compliance to voluntary professional standards prompted the USP to convene the Sterile Compounding Committee in 2000 with the purpose of developing sterile compounding standards.

On April 29, 2002, the U.S. Supreme Court declared section 503A invalid in its entirety because it "contained uncon-

stitutional restrictions on commercial speech" (i.e., prohibitions on soliciting prescriptions for and advertising specific compounded drugs). This caused the FDA to become circumspect about inspecting and taking action against compounding pharmacies. It also prompted the USP to convene the Sterile Compounding Committee in 2000. In Jan. 2004, Chapter <797> Pharmaceutical Compounding-Sterile Preparation was published in the U.S. Pharmacopeia and became the first practice standard for sterile pharmacy compounding in U.S. history enforceable by the FDA and state boards of pharmacy. This standard, referred to by some as "good compounding practices," is similar to current GMPs in their organization, but are significantly less stringent and have not been vigorously and actively enforced by the state boards of pharmacy.

Since USP Chapter <797> was published, compliance is only required by law in 23 states. Since the NECC event, however, state boards of pharmacy have undertaken a massive effort to provide training to ensure that staff are qualified to perform sterile compounding inspections and are inspecting pharmacies in order to detect bad practices. The FDA has also been extremely busy visiting pharmacies, having inspected and issued Form 483s to over sixty compounding pharmacies and five contract testing laboratories. These pharmacies were inspected against current GMPs, although many of them were not registered with the agency and not expected to comply with 21 CFR 210 and 211. The FDA did not inspect these operations against the USP chapters on compounding. Several pharmacies issued drug recall notices due to concerns associated with quality control procedures that present a potential risk to sterility assurance that were observed during recent FDA inspections of the pharmacy or because of testing errors at contract testing laboratories.

Today, only one in six pharmacy graduates is prepared for sterile compounding work

On Nov. 27, 2013 the Drug Quality and Security Act was signed into law **[Editor's Note:** See story on p. 37 for an overview of the new law**].** The purpose of this act is to amend the Food, Drug, and Cosmetic Act with respect to human drug compounding and drug supply chain security. The passage of this law will reinstate federal compounding language from Section 503A of the 1997 FDA Modernization Act. The unconstitutional advertising provisions in the original 503A law were removed, providing the FDA with the ability to start differentiating legitimate compounding pharmacies from organizations that were manufacturers but practicing under the guise of pharmacies. The law is significantly different than the original proposed Senate bill, which would have afforded both the FDA and state boards of pharmacy clarity on regulating the outsourced compounding industry. Pharmacists have both a moral and professional obligation to embrace USP Chapter <797> as the national standard practice that can ensure that compounded medications are safe when followed. Depending on their individual state pharmacy rules and regulations, they have also have a legal obligation to comply with USP Chapter <797>.

Embracing a Quality System

USP Chapter <797> provides a robust quality system to ensure that compounded injectable medications are safe for patients. It must also undergo constant revision in order to incorporate the latest and best science. Many of the quality challenges that the pharmaceutical industry struggles with like sterility testing also affects pharmacies to get greater degree because of many of the USP compendial tests are industrial standards and difficult to down-scale to small batch sizes. This poses a challenge for pharmacists to meet the future state demands of patient care.

Compounding and Future Pharma

On the subject of small batch sizes, it can be argued that compounding shares similarities with the development of personalized medicines, which are also delivered in small batches. Genomic re-

Recent U.S. FDA Guidances Related to New Law

Upon passage of the Drug Quality and Security Act, the U.S. FDA released the following draft guidances:

Registration for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

This draft guidance is intended to assist human drug compounders that choose to register as outsourcing facilities in registering with FDA. The draft guidance provides information on how an outsourcing facility should submit facility registration information electronically.

Interim Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act

The draft guidance addresses new provisions in the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Drug Quality and Security Act (DQSA), and sets forth an interim electronic submission method for human drug compounders that choose to register as outsourcing facilities.

Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act

The draft guidance announces the Agency's intention with regard to enforcement of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to regulate entities that compound drugs, now that the FD&C Act has been amended by the Drug Quality and Security Act. When final, the guidance will reflect the Agency's current thinking on the issues addressed by the guidance.

search and pharmacogenomics over the past ten years has identified how genes affect individual responses to medicines. The therapeutic effect of the medication can depend, to a certain extent, on your genes. This knowledge is being used to improve the safety of medications and enhancing their therapeutic efficacy. As physicians start applying pharmacogenomics to ensure that the patient receives the right drug at the right dose, the pharmaceutical industry will respond with FDA-approved medication. The need and demand for compounded and personalized medication will grow significantly over the next decade regardless of how pharmaceutical manufacturers respond to these medical advances. Pharmacists will need to employ robust quality systems so that a patient's therapeutic needs can be met while simultaneously ensuring that any compounded medication is sterile and accurate. A partnership between the pharmaceutical industry, scientists and practitioners must be fostered in order to advance the quality systems needed for just-in-time and small batch compounding that will be required to care for patients.

References

1. Hellums, M., Alverson, S.P. and Monk-Tutor, M.R. "Instruction on compounded sterile preparations at U.S. schools of pharmacy." *American Journal of Health-System Pharmacy* 64 (2007): 2267-2274
2. Multi-State Meningitis Outbreak - Current Case Count, Centers for Disease Control and Prevention: October 23, 2013 www.cdc.gov/hai/outbreaks/meningitis-map-large.html
3. Sterile compounding tragedy is a symptom of a broken system on many levels. *ISMP Medication Safety Alert! Acute Care*, October 18, 2013 www.ismp.org/Newsletters/acutecare/showarticle.asp?id=34
4. Burton, Thomas M., Grimaldi, James V. and Martin, Timothy W. "Pharmacies Fought Controls: Industry at the Focus of Meningitis Outbreak Beat Back More Federal Oversight." *The Wall Street Journal*, October 14, 2012. online.wsj.com/news/articles/SB10000872396390444657805780529722304040 46 (accessed December 2, 2013)

[Editor's Note: The topic of the sterile compounding of pharmaceuticals will be a topic of discussion during a roundtable breakfast session April 8 at the *2014 PDA Annual Meeting* in San Antonio, Texas. Visit pdaannualmeeting.org for more information.**]**

About the Author

Eric Kastango has dedicated his life's work to patient safety through better pharmacy sterile compounding, lean production and quality management practices.

Quality Metrics Conference Shapes PDA Agenda

Walt Morris, PDA

On Dec. 9–10, PDA held the well-attended and received *2013 PDA Pharmaceutical Quality Metrics Conference* in Bethesda, Md., featuring lively discussions and interactive workshops.

Over 300 industry experts on drug product quality and manufacturing assembled to participate in breakout discussions and select the most important and useful quality metrics. The interactive sessions were set up to assist a PDA task force draft a points to consider report on pharmaceutical quality metrics, which PDA intends to submit to the U.S. FDA in December.

A large number of CDER officials also attended the meeting, including Director **Janet Woodcock,** MD.

Woodcock took the podium in the closing session and thanked PDA for holding the workshop. "This is really important. We are having an ongoing dialogue about this issue of metrics. I was able to come and listen to the report-out from the polls and breakout sessions. I was very intrigued by both the engagement and what people actually said about what is going on. It gave me a lot of hope that we can really make this happen," she said.

In closing the conference, PDA President **Richard Johnson** assured participants that the feedback received greatly helped the PDA task force refine its points to consider report, which will be sent to the FDA before the end of 2013.

"Whatever the team was thinking before the meeting, I can assure you it is different today… If it was easy, we wouldn't need a meeting."

Moving forward, Johnson pledged that PDA "will invite and try to work with other organizations in the coming year to harmonize, specifically, some definitions of some of these metrics so as we move forward at least that is not a barrier."

"We already had a discussion within PDA to do a blinded survey of these draft metrics that we are going to pull together so that companies can self-report and we can share the results in a blinded way with companies. A beta test to see if we identified things that are going to be meaningful to differentiate."

PDA Pharmaceutical Quality Metrics Committee

Steve Mendivil, *Chair, Amgen*
Ian Elvins, *Consultant, PDA BOD*
Anil Sawant, *J&J, PDA RAQAB*
Anders Vinther, *Genentech, Chair PDA BOD*
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Joyce Bloomfield, *Merck, PDA BioAB*
Bob Kieffer, *Consultant*
Vince Anicetti, *Boehringer Ingelheim*
Denyse Baker, *PDA*

Continued at bottom of page 32

PDA Members Discuss Compounding Events' Impact on Industry

The following is a discussion among PDA members about the impact of the pharmaceutical compounding problems that surfaced in 2012/2013 and the impact on industry. The discussion occurred during the Q&A following the opening plenary presentations at the 2013 PDA Aseptic Processing-Sterilization Conference *in Chicago, Ill., June 20–21. This discussion is abridged for space considerations. The full transcript of the proceedings, including slides, is available at the PDA Bookstore, www.pda.org/bookstore.*

Glenn Wright: …What do you think this recent pharmacy issue has done to the reputation of our industry, not only within the U.S., but globally? You know, a lot of us have thought about countries where we say, "Boy, you sure wouldn't want to make a pharmaceutical there," right? So why has that had an impact?

Then for Robert, I'd like to ask a question. What do you think the impact of not having microbiologists in these compounding pharmacies—do you think that's a possible cause? So I'll leave those with you.

Hal Baseman: …I don't know what the public is thinking, but there appears to be a blurring between compounding pharmacy incidents and sterile production coming out of manufacturing companies in the public's perception. And that was, if you watched the Senate testimony at the Senate hearings with Commissioner Hamburg there, you could see that. You could almost see the frustration there that this is different than traditional manufacturing.

Again, having people in the public domain, friends of mine that would say, "Wow! What's going on with sterile products? They're not safe anymore?" So there is this blurring, and I don't think it helps the reputation of what we do…

Robert D. Seltzer: I'd like to add it may not be always practical to have a microbiologist at such a small-scale compounding operation; however, I just thought about it that the compounding pharmacist should probably be required to have either additional certification in certain amount of the body of knowledge of the microbiologist; for instance, knowing the origin of contamination and be able to manage the risks of contamination sources, knowing all the routes of contamination, the failure modes that lead to contamination…

Peter Noverini: …How do we shepherd and foster this philosophy, as Bob had mentioned, do no harm and really create a quality-based organization within these compounding pharmacies?

Hal Baseman: …I think that the body of knowledge that Bob talked about in regards to all the great things that PDA and other societies have is certainly out there, and the design of these facilities, procedures, training are certainly…not mysteries. And these are still smaller operations that could be easily controlled, but just have to be incentivized to ask for that advice and take it.

What we can do at societies like PDA is sort of reach out….The fact that they're not here is not just sort of a criticism to them, but maybe we need to reach out a little more, and you guys as vendors, with all the great products and control systems you have, perhaps that something you could reach out a little more too.

Attendee: On behalf of the pharmacists—I don't know how many pharmacists are here. Myself, I'm a pharmacist, and I can say that pharmacists have a very rounded education, scientific education. We take several courses in compounding. At least when I studied at my school, we had several courses in compounding. We were required to have microbiology and bacteriology courses, so we have a very rounded education that's ideal for the pharmaceutical industry. I just wanted to make that clarification.

Robert D. Seltzer: Well, if I can, because I think it's a good point, but I think the challenge is that the type of training that applies to making individual doses and the kinds of challenges that you get when you start making larger batches, that's more the kind of training that people who are in the industry are getting, maybe not so much in the pharmacy school, because we've—we deal with this all the time. I mean, that's why we have the Technical Report on Manual Aseptic Processing, but in an industrial setting, we have other methods and controls that we have to learn in the industry because, frankly, there are not a lot of schools that are teaching that.

But I think that the point is what we need maybe to reach out more is that the people who are doing that activity that is kind of going over the line into more of an industrial process, that they become aware that, yeah, there are people who know something about how you can do that in a better controlled way and make sure that they are taking advantage of that.

Quality Metrics Conference Shapes PDA Agenda continued from page 32

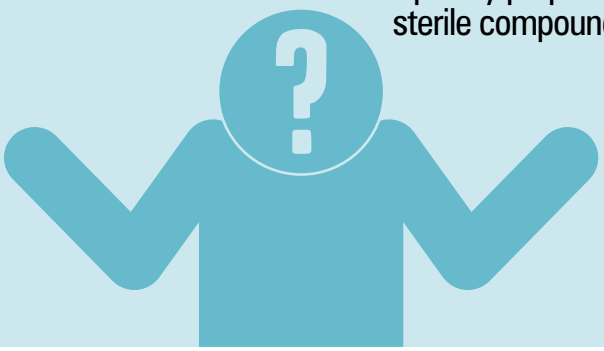
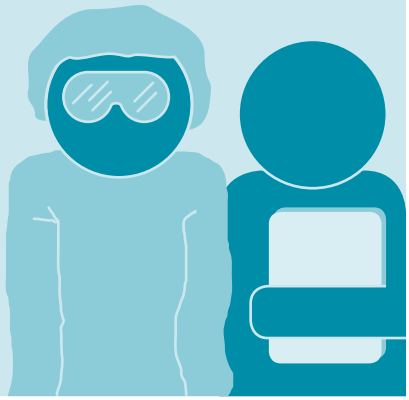
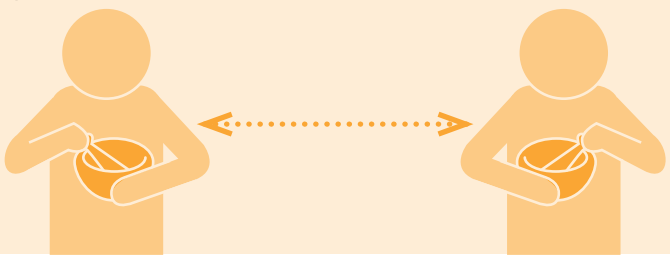
Johnson noted PDA's readiness to conduct a pilot program to identify issues and challenges that would need to be addressed prior to the rollout of an official U.S. FDA metrics program.

The data from the survey and the pilot will be used to help assess the robustness of the proposed definitions, the ease and availability in which the data is collected, and the knowledge and value gained from the data reported.

Finally, Johnson indicated that PDA is considering a follow-up *Pharmaceutical Quality Metrics Conference* in 2014.

[Editor's Note: See the PDA Photostream for photos of this event. The February issue will delve deeper into the proceedings of the confernece and include highlights from the PDA Points to consider document, submitted to FDA in December following the conference.**]**

PDA Offers Solutions for Compounders

Problem	Solution
Compounded products have been voluntarily recalled due to lack of sterility assurance. 	 *PDA's Technical Report No. 62: Recommended Practices for Manual Aseptic Processes* offers methods for controlling and evaluating aseptic processing operations.
Few pharmacy graduates are adequately prepared for sterile compounding. 	PDA's Training and Research Institute offers a lecture- and lab-based course on aseptic processing. 
Compounders often work with small batches which present different challenges from manufacturers working with larger batches. 	Members of **PDA's Clinical Trial Materials Interest Group** also work with small batches. Networking with members of the group offers opportunities to learn more about specific challenges in this area, particularly when working with outsourced material. tinyurl.com/ClinicalTrialMaterialsInterest 

Where do leading experts turn to communicate with the PDA community?

The *PDA Letter* and *PDA Journal of Pharmaceutical Science and Technology*

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snapshot

RAQAB *Update*

RAQAB Quarterly Report Q4 2013

Ruhi Ahmed, PhD, Ultragenyx, Denyse Baker, PDA, Jahanvi (Janie) Miller, PDA

QRM Technical Reports

The *2013 PDA/FDA Joint Regulatory Conference* in September marked a milestone for the quality risk management (QRM) series of technical reports for RAQAB. This series delivers a broad spectrum of case studies and industry application of QRM beginning with *Technical Report No. 54: Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations* supplemented by three annexes:

Annex 1: Case Study Examples for Quality Risk Management in Packaging and Labeling (Published 2013)

Annex 2: Case Studies in the Manufacturing of Pharmaceutical Drug Products (Published 2013)

Annex 3: Case Studies in the Manufacturing of Biotechnological Bulk Drug Substances (To be Published in 2014)

The published technical reports can be found at the Paradigm Change in Manufacturing Operations (PCMO[SM]) home page (dossier): www.pda.org/pcmo/dossier.

In light of the exceeding discussions on drug shortages, it was decided that a team be formed to develop risk-based approach for ensuring sustainable supply, adding to our portfolio of QRM-based technical reports as a PCMO[SM]-sponsored project.

RAQAB Sets Goals for 2014

During the November meeting, RAQAB identified improving connections with interest groups and chapters as one of their goals for 2014. Possible activities include providing speakers and establishing communication channels to collect "hot topics" and areas of concern from these members for possible PDA response. Other goals include developing a regulatory commenting process for BRICK countries, exploring ways to promote a "speak up" quality culture across industry and responding to the continuing FDASIA and EU Falsified Medicines Directive implementations.

PDA Comments Provided for the EU Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev 1)

An RAQAB expert task force recently commented on the proposed EU Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev 1). This guideline describes the general principles to be applied for similar biological medicinal products (also known as biosimilars), and addresses the application of the biosimilar approach, the choice of the reference product and the principles of establishing biosimilarity.

The issue of what constitutes "biosimilarity" is of critical importance to both the opposition and the supporters of biosimilars in the pharmaceutical biotechnology industry. Therefore, the proposed EU guideline is anticipated to have a wide ranging impact on the regulatory landscape that is currently being defined for biosimilars and the associated expectations for obtaining marketing authorization.

The majority of the PDA comments **[Editor's Note:** See page 43 to view the PDA cover letter sent to the European Commission**]** aimed to enhance clarity and consistency in the proposed EU guideline. Specifically, when defining a biosimilar medicinal product, compliance to existing definitions and guidance provided in Directive 2001/83/EC, Annex I and EU Guideline on Similar Biological Medicinal Products containing biotechnology-derived proteins as active substance: quality issues (EMEA/CHMP/BWP/49348/2005), was requested. The comments for consistency particularly addressed the need for including the recognition and significance of the manufacturing process in ensuring the quality and comparability of a biosimilar.

The proposed EU guideline is curiously deficient on the criticality or the impact of the production process in the manufacturing of biosimilars, even though it is explicitly stated in the above-mentioned EU guideline (EMEA/CHMP/BWP/49348/2005): that a "… similar biological medicinal product is defined by the following two sets of characteristics: 1) related to the characteristics of the molecule (including product related substances/ impurities), and 2) related to its process (which may affect molecular characteristics and includes process related impurities)."

We trust that the reviewers at the Committee for Medicinal Products for Human Use will take note of the discrepancies highlighted by the PDA team in their comments and will address them appropriately.

New Law Targets Compounding, Traceability

Alan Burns, Teva

On Nov. 27, a new law governing the safety of the nation's drug supply was signed.

The Drug Quality and Security Act adds clarity to the U.S. FDA's authority to regulate drug compounding. Although Congress had been working on drug security and traceability for several years, compounding pharmacy issues drew the public's ire following a series of fatal meningitis outbreaks last year caused by drugs produced in a compounding pharmacy. Previously, compounding pharmacy oversight was mostly a state responsibility, with limited FDA oversight.

The legislation draws a distinction between traditional compounding pharmacies and those that ship sterile products across state lines. It also creates uniform federal standards for key supply chain stakeholders and a national system of serialization to effectively trace drugs throughout the supply chain, replacing the existing patchwork of state pedigree rules.

Improved Agency Oversight

Compounding pharmacies that ship product across state lines are to be identified as "outsourcing facilities." These entities will be regulated by FDA but remain exempt from the bevy of regulations that apply to traditional drug manufacturers. Traditional compounding pharmacies will continue to be regulated by state boards of pharmacy. Congress views that market forces will provide incentives for facilities to participate in the program since hospitals, healthcare facilities and other providers will likely prefer to purchase compounded drugs from regulated entities.

According to the provisions of the Act, outsourcing facilities will be required to register with FDA each year, and FDA will make public the listing of registered facilities. Outsourcing facilities must pay user fees to FDA and meet a series of reporting and other quality assurance and regulatory requirements. Every six months, the facility must submit a report to FDA that, among other things, identifies the drugs compounded at the facility. In addition, outsourcing facilities will be subject to FDA inspection based upon a risk-based approach to be developed by the agency. Similar to existing agency approaches, inspection determinations will be based on the known safety risks of outsourcing facilities based on compliance history, the number of recalls linked to the facility and the inherent risks of the drugs compounded at the facility. Facilities are also required to submit adverse event reports to FDA. Pharmacies that choose not to participate in this program remain subject to state pharmacy licensure rules.

State boards of pharmacy are required to submit to FDA any actions taken against outsourcing facilities and inform the agency of any concerns that a facility may be operating outside of FDA requirements. This includes state board actions, sanctions, suspension or revocation of a state license. Likewise, FDA is required to notify a state pharmacy board if it finds that an outsourcing facility is in violation of federal regulations.

Improved Drug Security

The act also creates a new federal system of traceability for prescription drugs, badly needed to improve the outdated state-to-state system. The legislation implements a national unit level serialization program by requiring manufacturers to use a product identifier with each individual package and homogenous case of the product in four years. Repackagers are required to affix product identifiers to products within five years, and are also required to use interoperable electronic unit-level product tracing in ten years. The unit-level product tracing requirements will be based on guidance issued by FDA regarding standards for interoperable data exchange.

[Editor's Note: See cover story on p. 28 for a history of compounding.]

About the Author

Alan Burns has held a number of quality management roles in the pharmaceutical industry for more than twenty years. His expertise includes aseptically processed, lyophilized, and terminally sterilized drug products, as well as solid dosage units.

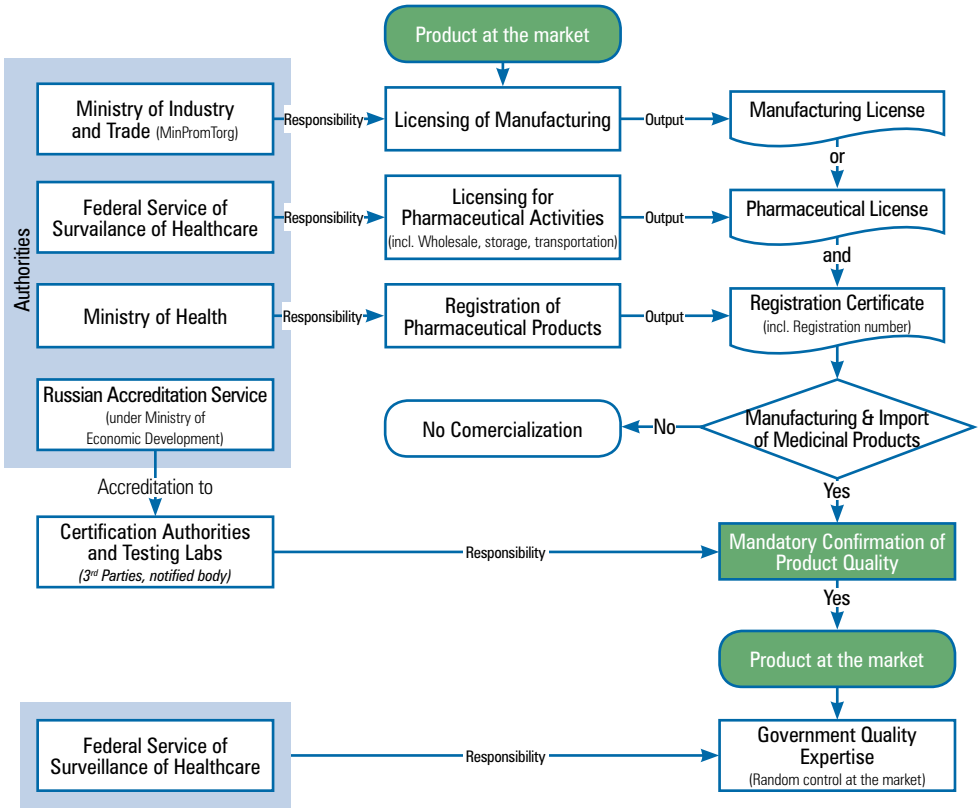
Manufacturers Face Certification, Licensing Steps in Russia

Elizabeth Meyers, Amgen, Natalya Parfenova, District Quality Control Center, and Stephan Roenninger, PhD, Amgen

In Russia, the commercialization procedure for medicinal products is decentralized, resulting in a process that's complicated to follow due to an ever-changing regulatory environment. Several independent regulatory authorities are involved in overseeing the quality of products, which includes issuing of marketing authorizations, licensing of manufacturing facilities (including warehouses) and certifying quality of medicines prior to entering the commercial supply chain **(Figure 1).** Examples of these regulatory authorities include: the Ministry of Health and the Federal Service for Surveillance in Healthcare, or Roszdravnadzor (RZN); the Ministry of Industry and Trade of the Russian Federation (MinPromTorg) and the Ministry of Economic Development. In addition, accredited testing laboratories play a key role in the process of registration, inspections, initial and routine market entry as well as the quality surveillance of medicinal products on the market.

The federal regulation, "On Licensing of Certain Types of Activities" ***(1)*** sets forth licensing requirements. In accordance with Article 12 of this legislation, "The List of Activities Subject to Licensing," manufacturing of medicinal products and pharmaceutical activities require licensing. Furthermore, the Government Directive on Licensing of Pharmaceutical Activities, defines "pharmaceutical activities" as retail and wholesale commerce, storage and transportation of pharmaceutical products. Licensing of pharmaceutical activities is performed by RZN, whereas licensing of pharmaceutical manufacturing is a responsibility of MinPromTorg. It is worth mentioning that licensing of manufacturing sites applies only to domestic manufacturers. Registration and mandatory conformity assessment of medicinal products, however, is required for domestic as well as foreign products. Mandatory conformity assessments can be satisfied through either certification or declaration of conformance. Independent, accredited certification centers (similar to the "Notified Bodies" in Europe) are authorized to assure compliance of medicinal products and to certify quality systems of manufacturers.

Figure 1 Russian Authorities and Commercialization of Medicinal Products in Russia



The Russian Pharmacopeia is referred to during the registration and quality control testing. Interestingly, Russia is an observer in the European Pharmacopoeia as part of the European Directorate for Quality of Medicines. This observership allows for participation in the scientific work of the respective committees and the European Pharmacopoeia Commission, which is the decision-making body for this Pharmacopoeia. In addition, the United States Pharmacopoeia (USP) is often used as a reference, as it has been available in Russian since 2009.

Just as the U.S. Department of Health and Human Services resides in the executive branch, the Ministry of Health of the Russian Federation (MoH) rests in the executive branch of the Russian government as well. This Ministry is responsible for registering of medicinal products and issuing of marketing authorization, in addition to many other functions.

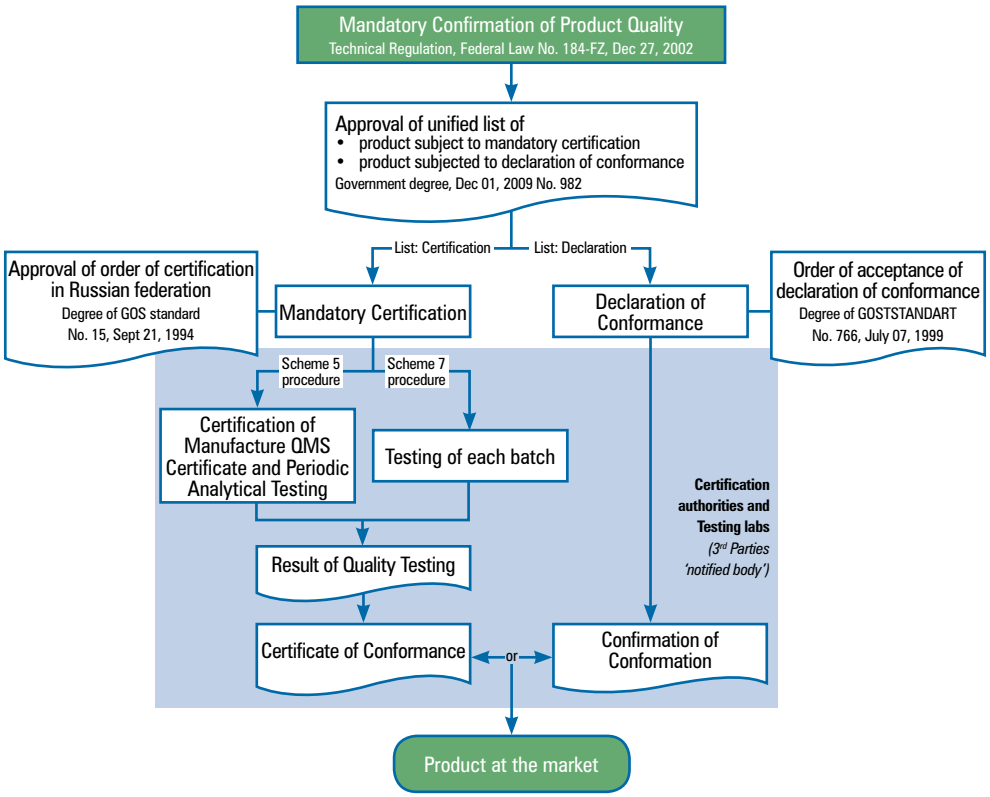
The expert evaluation of the dossier during the registration is performed by expert bodies/organizations reporting to the MoH. During this evaluation process, product samples are requested by the MoH along with reference standards and reagents to perform analytical testing. Since the MoH doesn't have its own laboratory, the preregistration testing is performed by independent authorized laboratories. The applicant is not allowed to conduct method transfer or provide training. Instead, it is expected that the expert laboratory performing the evaluation is capable of executing the testing based simply on the analytical methods submitted by the applicant in Russian. In addition to laboratory testing, expert evaluation of the product quality and product benefit/risk ratio includes review of CMC data. All of the expert evaluation results

are forwarded back to the MoH, which makes a decision on the product registration. In accordance with article 15 of the regulation, "On Circulation of Medical Products" ***(2),*** preregistration expertise of medical products resides with the Federal State Institution for the Examination of Medical Products. In addition, selective control of medicinal product quality could be performed during the marketing of the product on regular basis ("selective control"). This control is performed by authorized RZN laboratories (the list of these laboratories is available on RZN website).

Manufacturers need a medicinal products manufacturing license to produce medicines in the RF and a different ministry is involved in the licensing process of manufacturing facilities. Granting these licenses used to be a responsibility of RZN, but after the implementation of a regulation ***(1)*** covering the circulation of medicines, the function of medicinal products manufacturing licensing was handed over to the MinPromTorg. All requirements are provided in the decree, "On Approval of Rules of Licensing of Medicines Manufacturing" ***(3).*** In addition to licensing of manufacturers, MinPromTorg is currently tasked with creating a Russian version of GMPs. GOST R 52249-2009 ***(4),*** is an exact translation of *EudraLex - Volume 4 Good Manufacturing Practice Guidelines.* The enactment of this standard is expected by the end of 2013, although it could be further postponed.

Even after preregistration quality testing, the product is subject to mandatory conformity assessment through certification, per the regulation, "On Technical Regulation" ***(5).*** The Russian government ensures control of the medicines' quality and safety by requiring the certificates or declaration of conformance. According to the regulations ***(1),*** medicinal products should be certified in the form of adoption of Declaration of Conformity in the Certification Centers, accredited by Federal Agency for Technical Regulation and Metrology **(Figure 2).** The list of products subject to certification is outlined in this decree and periodically updated. Interestingly, this list includes not only medical products but extends

Figure 2 Mandatory Confirmation of Product Quality



to a large variety of industrial materials, ensuring that these items meet standards for entry to the Russian market.

In a case where compulsory certification or declaration of conformance is required, the product samples are sent for laboratory analysis, performed by authorized laboratories, accredited by the Russian Federal Accreditation Services, which publishes and maintains the list of authorized laboratories.

The Russian Federal Accreditation Services is part of the Russian Ministry of Economic Development, similar to how the National Institute of Standards and Technology is part of the U.S. Department of Commerce. Based on the outcome of analytical testing, Certificates of Conformance are issued by accredited Certification Centers.

When comparing the certification process in Russia with pharmaceutical products quality requirements in the United States or European Union, one can see greater differences than similarities. In the United States and Europe, manufacturers are entrusted with certifying the quality of their products and releasing them to the market, however, in Russia there is much greater government involvement. Remarkably, the closest parallel to the Russian certification process is the Declaration of Conformity (DoC) for medical devices carrying the CE marking in the European Union. In this case, an EU Notified Body is an organization that has been accredited by a Member State to assess whether a product meets quality standards. This organization is empowered to certify that a medical device conforms to the EU Medical Devices Directive, which defines the standards for medical devices. With a DoC, the manufacturer can label the product with the CE Mark, which is required for distribution and sale in the European Union.

Similar to Notified Bodies, Certification Centers are accredited by Russian Federal Accreditation Services to evaluate the quality of medicinal products and issue a Certificate of Conformance. Examples of such Certification Centers in Moscow are District Quality Control Center and the Federal Center of Expertise and Quality Control of Medicinal Products. Along with issuing Certificates of Conformance, these Centers are accredited to certify Pharmaceutical Quality

TRI Shares Expertise With SPCPA Delegation

On Oct. 24, members of the St. Petersburg Chemical and Pharmaceutical Academy in Russia visited PDA's Training and Research Institute as part of the Academy's initiative to build a training center in St. Petersburg (see story on p. 7 of the May 2013 issue).

Academy representatives **Alexey Marchenko, Nataliya Lebed, Yulia Perova** and **Tatiana Buldakova** were gracious to answer the following questions for the *PDA Letter:*

1. *What are the goals of the St. Petersburg Chemical and Pharmaceutical Academy in establishing a training center for pharmaceutical professionals, both in government and in the private sector, in St. Petersburg?*

   International GMP standards will be introduced in Russia at the beginning of 2014. This will make the issue of training the Russian GMP Inspectorate vital. We expect that this particular problem will be solved with the help of GMP center in Saint Petersburg. In addition, the center will be able to give opportunities for domestic and foreign pharmaceutical companies to improve the skills of their staff.

2. *Will the Center focus primarily on the industry in and around the city, or does it hope to serve members of the industry throughout Russia?*

   The training center will focus on training of specialists from Russia and from Commonwealth of Independent States countries.

3. *How comparable will this training facility be with PDA's Training and Research Institute? If very similar, will it include hands-on GMP processes, like a clean room and testing labs? If not as extensive, will it include lecture space? And if so, would it accommodate multiple lectures at one time?*

   We are proud that we were the first specialists from Russia, who have been trained at PDA, and were able to get acquainted with the unique simulator aseptic that meets GMP requirements. We will create a training center in St. Petersburg that takes into account best international practices and the needs of the modern pharmaceutical industry.

4. *What is the timeline for establishing the center? What are your next steps when you return to Russia?*

   The center is in the design stage now. After training and returning to Russia, we plan to share the experience with our colleagues at the Academy and continue working on the project.

5. *Once your training facility is in place, do you see private sector professionals benefitting from it as much as regulatory inspectors and SPCPA students?*

   It is planned that the activities of the GMP center will be directed to the widest possible audience of interested professionals and pharmaceutical industry.

6. *You plan to offer GMP-related courses. Do you have an initial syllabus already planned? Will these be modeled on existing PDA TRI courses?*

   We look forward to working closely with PDA specialists in the development of training programs.

Management System (QMS). Industry is arguing for reduced testing based on scientific understanding, as described in an International Federation of Pharmaceutical Manufacturers & Associations position paper on redundant testing ***(6).***

The certification is considered necessary to ensure that only high quality medicines enter the market and to prevent the substandard medicines reaching the patient. This process, however, is lengthy and expensive, causes increased operating costs, cuts into product shelf life, and most importantly, delays product availability to patients. Furthermore, there is no clear pathway to investigating Out of Specification results, if they occur. One way to reduce time and expense for testing of every batch of imported product is to obtain a Quality Management System Certificate from one of the accredited centers. Therefore, it is in a company's interests to apply for voluntary certification of their QMS. The process includes applying for certification, paying a fee, and submitting quality system documents for review. All documents need to be translated to Russian. After the fees are paid and documents submitted, the applicant is required to host an on-site inspection of its manufacturing facilities. The inspections are conducted in the framework of ISO 9001:2008 (QMS) and GOST R 52249-2009 (equivalent to EU GMP) and after successful completion of the inspection of applicant's manufacturing sites a Certificate of Quality Management Systems is issued. This certificate exempts the company from certification testing of every batch. The testing frequency will be reduced and determined based on the number of imported batches per year. For example, only one out of ten imported batches per year will be tested if QMS certificate is obtained.

In conclusion, manufacturers planning to operate in the Russian market should prepare to navigate a tangle of unclear and emerging guidance and regulations. Some agencies and government organizations may appear to operate like their western counterparts, but their processes and responsibilities can be quite different. Moreover, manufacturers face a different type

(l-r) Viacheslav Bakulin, Eli Lilly; Nataliya Lebed, SPCPA; Yulia Perova, SPCPA; Tatiana Buldakova, SPCPA; Alexey Marchenko, SPCPA

of scrutiny than that found in the West. A major issue is the absence of legal basis for enforcement of GMP regulations at this time. Ultimately, more inspections by certification centers and other, various Russian authorities can be expected.

References

1. Federal Law 04.05.2011 N 99-FZ (as amended on 02.07.2013) "On Licensing of Certain Types of Activities"
2. Federal Law N 61-FZ of 12-Apr-2010 on the Circulation of Medicines
3. Decree N 686 of 06-Jul-2012: on "Approval of Rules of Licensing of Medicines Manufacturing"
4. GOST R 52249-2009 (GMP for RF)
5. Federal Law NO. 184-FZ of December 27, 2002 "On Technical Regulation"
6. "Appropriate Control Strategies Eliminate the Need for Redundant Testing of Pharmaceutical Products." International Federation of Pharmaceutical Manufacturers & Associations, April 23, 2013 www.ifpma.org/fileadmin/content/Innovation/Biotherapeutics/IFPMA_Position_Paper_on_Redundant_Testing_vF.pdf

About the Authors

Elizabeth Meyers is the Senior Manager at Amgen International Quality & External Affairs and is responsible for Russia and CIS.

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Stephan Rönninger, PhD is the Head of External Affairs Europe, International Quality at Amgen (Europe) GmbH.

Working Group Encourages Industry, Regulatory Dialogue

Stephan Rönninger, PhD, Amgen

On Nov. 26, **Emma Ramnarine, Stephan Roenninger**, PhD, **Georg Roessling,** PhD, and **Anders Vinther,** PhD attended the EMA Inspectors Working Group meeting on behalf of PDA. This meeting was attended by all 44 EU-competent authorities representing 28 member states, in addition to accession countries and observers, including the U.S. FDA representative from its Brussels office.

EMA Working Plan

The first presentation focused on the work plan, reviewing the year's activities on EU-GMP Chapter 2, the EU GDP guideline and public consultations on Chapters 3 (Premise and Equipment), 5 (Production), 6 (Quality Control), 8 (Complaints and Product recalls), Annex 16 (Certification by a Qualified person and Batch Release) and the dedicated facilities guideline (this will probably get published in Part 3 of the EU GMP guide). It was mentioned, in particular, that Chapter 5 also includes requirements for qualification of suppliers, GDP, and starting materials, i.e., excipients and APIs. The final guidance is expected to be published in 2015. Annex 16 and the GDP for APIs will be finalized in 2014.

Annex 15 on "Qualification and Validation" will be published for consultation. It was noted that the scope is bigger than the Committee for Medicinal Products for Human Use (CHMP) guideline on process validation. Public consultation is expected on Annex 17 in early 2014, following the Agency's Committee for Medicinal Products for Human Use guideline on parametric release and Real Time Release Testing. The GDP guideline for medicinal products is finalized and updated with minor corrections (see http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm).

Inspection in third countries performed by Mutual Recognition Agreement (MRA) countries will also be used; this is not part of the formal MRA contract. According to the updated "Compilation of Community Procedures on Inspections and Exchange of Information," which include new EU formats, EMA and EU National Competent Authorities will consider leveraging inspection information from trusted partners (including PIC/S).

There is a possibility that Annex 1 (manufacturer of sterile products) might be reopened, or a Q&A will address current concerns, which will align with changes in the European Pharmacopoeia by the European Directorate for the Quality of Medicines & HealthCare standards.

By collaborating with industry, EMA focuses on minimizing supply disruption due to quality defects and nonGMP compliance. EMA provided an update on the drug shortage workshop, where PDA will also participate as an interested party and presented the current status of the Paradigm Change in Manufacturing Operations (PCMO[SM]) project.

EXCiPACT Update

EXCiPACT is a certification scheme with ISO 9001 and additional GMP and GDP certification. It was highlighted that this is a supplier-initiated process to select an EXCiPACT-certified certification body, i.e., registered independent auditors. An independent certification board reviews audit results and issues a certificate.

Today, only audits delegated to a third party by Marketing Authorization Holders are allowed. EMA was asked to update the existing Q&A to differentiate from API, allowing flexibility for excipients. The presenter also encouraged EMA to consider splitting API and excipients in Chapter 5 by not using the term "starting material."

Rx-360

Rx-360's focus was explained, emphasizing the organization's focus on supply chain security through developing best practice working groups, issuing white papers and offering webinars. Rx-360 also monitors and shares regulatory information. Furthermore, Rx-360 supports auditing; this can result in a cost reduction of 25'000 EUR for the client and supplier site.

GDP for APIs/Medicinal Products

For GDP on APIs, the Active Pharmaceutical Ingredients Committee of the European Chemical Industry Council presented their how-to guide, which links ICH Q7 (equal to EU-GMP Part II which equals PIC/S GMP part II) , ISO 9001:2008, the draft EU GDPs and the respective WHO guideline. It was emphasized that repackaging and relabeling are manufacturing not distribution activities. The link to WHO guidelines was much appreciated.

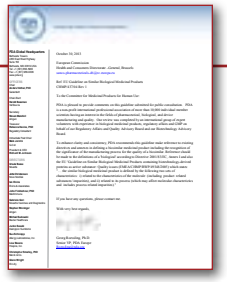
The European Federation of Pharmaceutical Industries and Associations stressed the duplication of guidelines in API EU GMP Part II (ICH Q7) and GDP only, clarifying that ICH Q7 is applicable. For the finished product, a clarification on Chapter 9 of the drafted guideline on transportation was requested. EFPIA's interpretation is that EU GDP embraces ICH Q9 and Q10 principles, and thus science- and risk-based approaches can be used to distribute product under limits broader than registered storage conditions. Temperature controls will be determined by the manufacturer based on a science and risk-based assessment. Decisions concerning transportation and storage temperature excursions can be made with regard to scientifically supported impact on product quality and/or potential degradation. Temperature monitoring of all shipments is not mandated as qualification of routes is permitted as part of defining the control strategy.

The Q&A session focused on the scope of the GDP for the API document. On

Continued at bottom of page 44

PDA Comments on EU Biosimilars Guideline

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



October 30, 2013

European Commission
Health and Consumers Directorate –General, Brussels
sanco-pharmaceuticals-d6@ec.europa.eu

Ref: EU Guideline on Similar Biological Medicinal Products

CHMP/437/04 Rev 1

To the Committee for Medicinal Products for Human Use:

PDA is pleased to provide comments on this guideline submitted for public consultation. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our review was completed by an international group of expert volunteers with experience in biological medicinal products, regulatory affairs and GMP on behalf of our Regulatory Affairs and Quality Advisory Board and our Biotechnology Advisory Board.

To enhance clarity and consistency, PDA recommends this guideline make reference to existing directives and annexes in defining a biosimilar medicinal product including the recognition of the significance of the manufacturing process for the quality of a biosimilar. Reference should be made to the definitions of a 'biological' according to Directive 2001/83/EC, Annex I and also the EU 'Guideline on Similar Biological Medicinal Products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/BWP/49348/2005) which states: "… the similar biological medicinal product is defined by the following two sets of characteristics: i) related to the characteristics of the molecule (including product related substances/ impurities), and ii) related to its process (which may affect molecular characteristics and includes process related impurities)."

If you have any questions, please contact me.

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

PDA Commenting Task Force

Barbara Jentges , PhACT GmbH (Chair)
Denyse Baker, PDA
John Geigert, PhD, BPQS
Wendy Zwolenski-Lambert, Novartis

Christopher Smalley, PhD, Merck

Hearing the Voice of Our Members

Although called "Voices of the Board," this is our platform to reflect back to you what we are hearing from your voices. We use many sources to be sure that we are listening to what you are saying—whether it is through the survey results we ask you following every major program, your participation in interest groups, your attendance and contribution to local chapters, your selection of Training and Research Institute courses, etc. As a member-driven organization, we are working harder than ever to listen to your voices to produce an array of offerings that meet your needs.

I want to focus on the Science element, but really all three elements work together. There is really such an amazing interplay between the three elements of this core focus. Starting with the concept of drug shortages, this clearly has a regulatory element not only because it deprives patients of needed medications, but because it also relates to the compounding pharmacy issue. How, you may ask? Because many times compounding pharmacies will attempt to fill the shortage by creating products that purport to be the same as the manufactured product. And how does this relate to the element of science? Because many times drug shortages are due to "aging facilities" or to older processes that have not been upgraded to more robust and reliable manufacturing systems. Now, these are the short and simple answers, so PDA has developed programs to provide the comprehensive answers in an interactive environment. These programs are possible only because PDA is able to draw on a wealth of Subject Matter Experts in both industry and regulatory.

PDA, as a sponsor of INTERPHEX in New York City, will be conducting three days of sessions on March 18–20 that will discuss bringing pharmaceutical and biopharmaceutical manufacturing into the 21st century. Continuing with this theme, the *2014 PDA Annual Meeting* program will include presentations on aging facilities, compounding pharmacies and emerging technologies.

Along with all of our workshops, conferences and courses, we have numerous teams working to bring out outstanding references to meet the needs you have identified. Recent technical reports have included not only Quality Risk Management (QRM), but reports that take QRM and demonstrate how to employ QRM using case studies, such as recent supplemental issues in packaging and labeling.

Other upcoming technical reports will address basics, offering great tools for internal training as well as benchmarking, such as reports on cleaning and disinfection. But this is only a sample of the large number of technical reports issued in 2013 and planned for 2014. All of these technical reports represent several years of effort on the part of volunteers like you, who are willing to devote their time to share knowledge and experience with the membership to resolve questions concerning the perceived conflict between regulation and science, best practices, and that all important element, making processes and products more robust and reliable.

We are working hard to listen to your voices!

Working Group Encourages Industry, Regulatory Dialogue continued from page 42

behalf of the team of inspectors **Ian Rees,** MHRA, referenced the introduction, suggesting that "distributors" are included in the scope. Ultimately, the Q&A will be published by the European Commission and not the Inspectors Working Group. Regarding the discussions on temperature during transport, there was a suggestion that if there is more data available, this could be used for a rational. The registered range should be followed. Plus, the supply chain might be very complex. Temperature loggers should be used according to the outcome of a risk assessment, especially if no one knows the temperature excursions experienced during the supply chain cycle.

Future meetings

Participants agreed that it is critical industry and regulatory work together to resolve inspection issues and that the agency receive feedback on problems. There could also be more dialogue before the meeting on common subjects. Issues could be identified among the work plan. Communication could better be channeled if topics are shared in advance, The structure of the meeting would benefit from separating presentations on positions from ones on data gathering.

[The author wishes to thank **David Coburn,** EMA, **Rebecca Stauffer,** PDA and **Emma Ramnarine,** Genentech, for their assistance**.]**

About the Author

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Upcoming Laboratory and Classroom Training for Pharmaceutical and Biopharmaceutical Professionals

MARCH 2014

Recommended Practices for Manual Aseptic Processes – *New Course*
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Fundamentals of Aseptic Processing
March 17-21 | Bethesda, Maryland
www.pda.org/apfundamentals

Aseptic Processing Training Program, Session 2 – March 31-April 4
Week 2, May 5-9 | Bethesda, Maryland
www.pda.org/2014aseptic

APRIL 2014

2014 PDA Annual Meeting Course Series
April 10-11 | San Antonio, Texas
www.pdaannualmeeting.org/courses

- Risk-Based, Product Development Basics for Combination Products: Harmonizing Design Controls and Quality-by-Design in Product Development and Market Authorization Documents – *New Course* (April 10)
- Biosimilars: Understanding the CMC Challenges of Meeting 'Similarity' – *New Course* (April 10)
- Implementation of Quality Risk Management for Commercial Pharmaceutical and Biotechnology Manufacturing Operations (April 10-11)
- Process Validation and Verification: A Lifecycle Approach (April 10-11)
- Quality Control and Quality Assurance of Cell-Based Therapeutic Products (April 11)
- Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Validation and Ongoing Control (April 11)

Validation of Moist Heat Sterilization Processes
April 15-17 | Bethesda, Maryland
www.pda.org/moistheat

PDA Biotechnology Week
April 21-25 | Bethesda, Maryland
www.pda.org/biotechweek2014

- Biopharmaceutical Manufacturing under Regulatory Compliance: Process Strategies, CGMP Considerations and Facility Requirements (April 21-22)
- Biosimilars – Understanding the CMC Challenges of Meeting 'Similarity' (April 23)
- CMC Regulatory Compliance of Biopharmaceuticals (April 24-25)

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April 28-30 | Bethesda, Maryland
www.pda.org/apmanagement2014

For more information on these and other upcoming PDA TRI courses, please visit www.pda.org/courses

Laboratory Courses

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

New Year, New PLEC Members, and Other Changes

One of the nicest things about having the *PDA Letter* Editorial Committee, which we formed in 2006 as part of our effort to transform a staff-written newsletter into a member-oriented magazine, is that we welcome new participants each year. While we miss the folks who participated over the previous two years, adding fresh voices and perspectives to the PLEC helps immeasurably in producing a high-quality and useful *PDA Letter.* Members can cycle back on to the committee, and have. In fact, **Robert Darius** and **Jose Caraballo** have rejoined the committee after serving in 2010-2011. We welcome them back! I also want to welcome the following new committee members:

- **Ross Acucena**
- **Mike DeFelippis**
- **Robert Dream**
- **Maik Jornitz**
- **Leticia Quinones**
- **Siegfried Schmitt**
- **Sherry Tamura**

Last year, we conducted the first-ever *PDA Letter* Readership Survey, and the response rate was fantastic, with nearly 10% of the membership participating. We learned a lot. Based on our initial assessment, we've decided to simplify the Letter a bit by removing the Programs & Meetings and TRI sections. Content regularly published in those sections will now appear in People, Science and Regulation. Look for more changes—including a new online presence—in 2013!

Speaking of membership and members, in this issue we highlight the ongoing struggles of compound pharmacy groups in complying with basic GMP and sterility assurance principles. PDA members spoke about the situation and the potential harm it can do to the perception of safe medicines in America at several meetings in 2013. We've included a transcript of one such discussion, which took place at the *2013 PDA Aseptic Processing-Sterilization Conference.* In addition, our cover story provides a primer on pharmaceutical compounding in the United States, the compliance issues that have surfaced, and the regulatory solutions being explored. The January Infographic highlights ways PDA, through the work of its members, can help pharmacy compounders meet the regulations and improve their sterility assurance practices. Finally, recent U.S. laws and subsequent U.S. FDA regulations are highlighted in the Regulation section.

Before we forget entirely about 2013, the PDA Photostream includes photos from four fall PDA conferences. These successful events brought together nearly a thousand PDA members to discuss current issues on a variety of topics. Reports from the *8th Annual Global Conference on Pharmaceutical Microbiology* and the *2013 PDA Pharmaceutical Quality Metrics Conference* are also included in this issue. Work is already underway to provide more extensive coverage of the Metrics Conference in the next issue.

We hope 2014 will be another successful year of providing (in the words of our readers) "analytical," "informative" and "thoughtful" content.

PDA Letter

The PDA Letter is published 10 times per year, exclusively for PDA members.

Subscriptions are not available.

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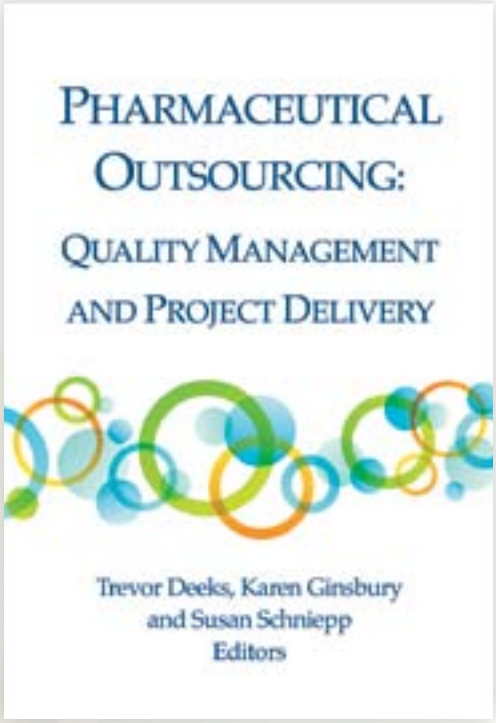
New Release at the PDA Bookstore



Item No. 17316

Pharmaceutical Outsourcing: Quality Management and Project Delivery

Edited by Trevor Deeks, Karen Ginsbury and Susan Schniepp

Many companies are looking to contract providers for managing various aspects of the drug development process. Contract organizations have services that range from research activities to clinical trial management and oversight to manufacturing of the clinical supplies and commercial product to packaging and labeling as well as product testing. Virtual companies may have multiple contracts with multiple service providers for multiple phases of the drug development process and the drug manufacturing process. To complicate the matter, there is little guidance from regulatory authorities regarding the use of contract providers. This book is intended to set forth and explore the best practices for contract organizations from various perspectives: the contract organization, the contracting organization and the regulators.

www.pda.org/outsourcing

The PDA Bookstore's Top 5 Best Sellers

1 Sterility Testing of Pharmaceutical Products
By Tim Sandle
Item No. 17315
PDA Member **$240**
Nonmember **$299**

2 Combination Products: Implementation of cGMP Requirements
Edited by Lisa Hornback
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3 GMP In Practice: Regulatory Expectations for the Pharmaceutical Industry, Fourth Edition, Revised & Expanded
By James Vesper
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4 The Bacterial Endotoxins Test: A Practical Guide
Edited by Karen McCullough
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5 PDA Technical Report No. 29, Revised 2012 Points to Consider for Cleaning Validation (single user digital version)
Item No. 43501
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The 2014 PDA Annual Meeting is the meeting place this April for ***the best*** content in the industry. The planning committee is formulating an exciting program addressing the current issues of our industry. They know your concerns, what you want to hear and who you want to hear it from.

PDA has established a long reputation of championing innovation and quality in the manufacture of biopharmaceuticals and sterile products and will bring you a wide variety of benefits that **focus on three key tracks:**

- Biological Sciences
- Product Manufacturing
- Quality Systems

There will be a number of keynote presentations that will include:

- **Opening Plenary Sessions** which will address innovative drug development approaches, and how transparent health technology assessments can recognize and reward the added value of new medicines while maintaining an innovation-friendly environment.
  - **The Impact of Technology on Vaccine Manufacturing and the Downstream Impact on Human Health**, Rahul Singhvi, ScD, Senior Vice President/ COO, *Takeda Pharmaceuticals International, Inc.*
  - **Patient Access to Treatment: How Clinical and Cost Effectiveness of Drugs can be Ensured**, Mark B. McClellan, MD, Director Health Care Innovation and Value Initiative, *Brookings Institute (invited)*
- **Plenary Session Two: Science and Innovation**
  - **Innovative Science and Future Benefits for Patients**, David Shanahan, President, *Mary Crowley Research Center* and President, CEO and Founder, *Gradalis*
  - **Cell and Gene Therapy**, Wilfried Dalemans, PhD, CTO, *TiGenix*
- **Closing Plenary: Emerging Technologies and Marketing**
  - **Emerging Markets**, Martin VanTrieste, Senior Vice President, Quality, *Amgen, Inc.*
- Poster Presentations
- Networking Receptions & Events like the 8th Annual PDA Golf Tournament at the AT&T Canyons Golf Course and the PDA 8th Annual Walk/Run
- Post-Conference Workshop: **PDA Bioburden and Biofilm Workshop** on April 9-10
- PDA's Training and Research Institute (PDA TRI) will be offering six courses on April 10-11

EXHIBITION: APRIL 7-8
POST-CONFERENCE WORKSHOP: APRIL 9-10
COURSES: APRIL 10-11

www.pdaannualmeeting.org