People • Science • Regulation

PDA Letter

Volume L • Issue 5 www.pda.org/pdaletter May 2014

Adapting Development Guidelines for Advanced Therapies 22

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Therapy Medicinal
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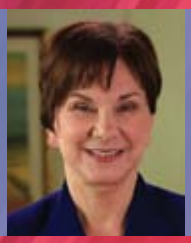
The Parenteral Drug Association presents the...

2014 PDA/FDA Joint Regulatory Conference

Connecting Regulatory, Quality, Science & Compliance: Assuring Customer-Focused Outcomes throughout the Product Lifecycle

September 8-10, 2014

RENAISSANCE WASHINGTON HOTEL | WASHINGTON, DC



JUST CONFIRMED

Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, *FDA*

The Food and Drug Administration and the Parenteral Drug Association are again planning the ***2014 PDA/FDA Joint Regulatory Conference.*** The objectives for this collaboration are to promote the adoption of more **robust design practices, quality systems** and **use of modern manufacturing technology** with the ultimate goal of improving medical products quality for the consumer.

Together these two organizations along with a number of other stakeholders are working to move manufacturers toward a future state that has been described as "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight. (**Janet Woodcock,** 2005)."

It is important that organizations continue to improve and adequately resource change management systems. This year the *PDA/FDA Joint Regulatory Conference* will address a number of topics that cover how further progress can be made toward drug manufacturing and quality objectives.

Immediately following the *2014 PDA/FDA Joint Regulatory Conference*, the PDA Training and Research Institute will be hosting six courses to complement your learning on September 11-12:

GMPs for Manufacturers of Sterile and/or Biotechnology Products (September 11)

Role of the Quality Professional in the 21st Century (September 11-12)

Application of a Quality Systems Approach (September 11-12)

Preparing for Regulatory Inspections for the FDA and EMA (September 11-12)

Quality by Design for Biologics:A Practical Approach – New Course (September 12)

Managing the QC and R+D Laboratory in a GMP Compliant Manner – New Course (September 12)

Visit **www.pda.org/pdafda2014** for more information.

EXHIBITION: SEPTEMBER 8-10 | POST CONFERENCE WORKSHOP: SEPTEMBER 10-11 | COURSES: SEPTEMBER 11-12

PDA Letter Call For Authors

The *PDA Letter* is looking for authors on the following topics:

Pharmaceutical Microbiology (due July 25)

Career Advancement (August 22)

Reports from the *2014 PDA/FDA Joint Regulatory Conference* (due Oct 7)

We're always interested in science and regulatory articles on aseptic processing, sterile products, supply chain and distribution, pharmaceutical microbiology, biologics and manufacturing quality control.

If you're interested, email Rebecca Stauffer at stauffer@pda.org.

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Parenteral Drug Association

PDA Letter

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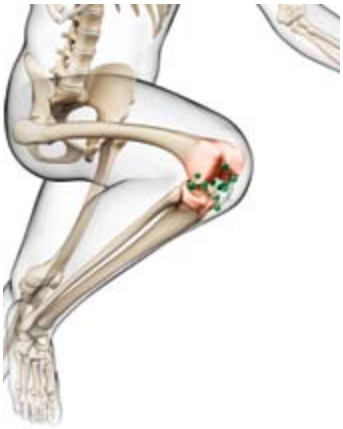
Cover



Cover Art Illustrated by Katja Yount

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Features

PDA Board of Directors Nominations Wanted

PDA members can nominate candidates for the Board of Directors election for the 2015–2017 term.

"We do not want to miss outstanding members of our organization and strive to have a diverse Board of Directors," says **Anders Vinther,** the current Nominating Committee Chair and Immediate Past Chair of PDA.

All PDA members are encouraged to nominate their peers within the Association for the Board of Directors election, although certain prerequisites are necessary. For example, only members in good standing can nominate and be nominated (that is, their membership is current).

The PDA Nominating Committee will consider all nominations and base their selection upon the following criteria:

1) Status of membership

2) Level of activity within PDA

3) Volunteer history

4) Length of membership

5) Diversity and relevant professional competence.

"When you nominate a candidate, please be so kind to include a brief explanation, which makes it easier for the selection committee to make their final choice," requests Vinther.

To nominate, send an email to: nominate@pda.org. Nominations for the 2014 BoD elections will be accepted through June 13, 2014.

U.S. FDA Experts to Answer Your Supply Chain Questions

PDA has confirmed the participation of four experts from the U.S. FDA in the upcoming *2014 PDA/FDA Pharmaceutical Supply Chain Conference,* June 3–4, 2014, at the JW Marriott in Washington, D.C.

The four FDA experts represent the Center for Drug Evaluation and Research (CDER) Office of Compliance Office of Drug Security, Integrity and Recalls (ODSIR):

- **Thomas Christl,** Office Director
- **Connie Jung,** PhD, Associate Director, Policy & Communication
- **Mark Paxton,** Regulatory Counsel
- **Steven Wolfgang,** Acting Associate Director, Risk Science, Intelligence And Prioritization

"PDA is pleased to once again provide industry representatives an opportunity to interact with representatives of the U.S. FDA at one of our regulatory meetings," said PDA President **Richard Johnson.** "This will be the fifth time PDA and the U.S. FDA have cosponsored a conference or workshop on the important issue of securing the supply of quality pharmaceutical ingredients and products."

The U.S. FDA speakers will field questions during the final plenary session on June 3**. Brian Johnson,** Sr. Director, Supply Chain Security, Pfizer, Inc., and chair of industry consortium Rx-360, will moderate the session.

Building on earlier PDA/FDA cosponsored conferences and workshops on pharmaceutical supply chains, the 2014 event will provide a forum to further implementation of innovative approaches to protect the quality of the product to the patient, and to prevent illicit acts such as counterfeiting, diversion, and economic adulteration from threatening the safety of the drug supply.

PDA Volunteer Spotlight

Amnon Eylath

- Senior Director, QA
- *Genzyme*
- Member Since | **1996**
- Current City | **Allston, MA**
- Originally From | **Brookline, MA**

Treat all people with respect regardless of their status or position

Why did you choose to join PDA?

I chose to join PDA based on the informative conferences, training and literature that PDA produces as well as the excellent global networking opportunities.

How has your work on PDA task forces contributed to your professional development?

My work at PDA has been recognized professionally at my workplace and has always been strongly supported.

What was your most distinctive memory from the *2013 PDA/FDA Joint Regulatory Conference?*

The session from the U.S. FDA's **Mary Malarkey** (Director, Office of Compliance) on how CBER wants its staff to make decisions based on risk assessments, so that they can focus resources more on what's most important in support of patient safety and drug quality.

What qualities do you like to see in a manager?

High personal and professional ethics, good communication skills, high level of emotional intelligence, and strong technical competency

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

I wish I'd known about how QA and Regulatory Affairs are excellent career paths for people coming out of college or graduate school.

What inspired you to choose your current career path?

I chose this path so that I would have the ability to help people and society live better lives, by working in the discovery and development of impactful medicines.

What are some of your hidden talents? When did you acquire them?

I can cook international recipes quite well. Learned cooking from watching the *Galloping Gourmet* TV show.

What is your favorite board game? Why?

Clue, since it takes some thinking and I always liked the characters in the game.

Register before July 28 and save up to $400!

The Parenteral Drug Association presents the...

2014 PDA Universe of Pre-filled Syringes and Injection Devices

October 6-8, 2014

HYATT REGENCY HUNTINGTON BEACH RESORT AND SPA
HUNTINGTON BEACH, CALIFORNIA

Have you noticed that terms like "patient centric design," human factors," and "patient outcomes" are becoming the hot topics of the day in our device world? Do you know how to incorporate that kind of thinking into your development projects? Have you been able to keep up with all the new technologies and devices entering this marketplace?

The device world is ever changing, especially now more than ever. In just two days you can get a crash course on the latest developments and hear how many of your peers have dealt with these challenges by attending the *2014 PDA Universe of Prefilled Syringes and Injection Devices Conference*.

You can expect to hear an array of topics, such as:

- Quality Infrastructure and Issues
- New Technologies and Trends in Manufacturing Processes
- Case studies
- Human Factors/Usability
- Injection Devices: Critical Attributes and Risk Management
- Regulatory and Compliance Aspects Such as Combination Products
- New primary Containers, Safety Devices, and Delivery Systems
- Global Market Trends

POST CONFERENCE WORKSHOP: 2014 PDA Drug Delivery Combination Products Workshop
October 8, 2014 | HYATT REGENCY HUNTINGTON BEACH RESORT AND SPA | HUNTINGTON, CALIFORNIA

Listen to the real life experiences of pharmaceutical professionals detailing the challenges they faced during development, approval and manufacturing of their Drug Delivery Combination Products. Interact with the participants in panel discussions where you will hear the differences discussed as to what has worked, what will no longer work and what strategies are likely to succeed in the future.

www.pda.org/drugdelivery2014

The PDA Training and Research Institute will be hosting four courses to complement your learning on October 9-10, 2014.

- Prefilled Syringe User Requirements – *New Course*
- Syringes and Elastomers: Understanding the Effects on Quality and Demonstrating the Production Process, Influences and Needs
- Technical and Regulatory Challenges of Drug Delivery Combination Products – Prefilled Syringes, Autoinjectors and Injection Pens – *New Course*
- Risk Management for Temperature Controlled Distribution

For more information and to register, visit **www.pda.org/prefilled2014**

EXHIBITION: OCTOBER 6-7 | COURSES: OCTOBER 9-10

chapter update

Australia Chapter Tours BFS Facility

Kim Waters, GSK Australia

On March 18, PDA's Australia Chapter coordinated a tour of a Blow/Fill/Seal facility for 59 attendees. There was quite a bit of interest due to the specific requirements for manufacturing BFS technology. Anyone who has led a production facility tour would understand that leading 59 people around is quite difficult, so attendees were divided into two groups.

Philip Leslie, gave an introduction to BFS, its applications and cost benefits. His passion for this technology was evident as he explained its potential uses, and most importantly, how it can be an avenue to provide low cost medicines to those who can least afford it. He then discussed the company's collaboration with Monash University and shared the experiences and benefits of this union. Attendees were able to gain an insight into how the younger generation at university can play an important role in industry.

Mark Hall and **Richard Friar** showed the groups around the Rommelag filling machine and the Shubert packing line. There was much interest and plenty of questions which kept both Mark and Richard very busy.

Thank you to Philip, Mark and Richard for hosting the first PDA Australia Chapter Event at GSK Australia.

PDA Who's Who

Philip Leslie, Site Technical Lead, GSK Australia

Mark Hall, Project Manager, GSK Australia

Richard Friar, Senior Project Engineer, GSK Australia

Philip Leslie (left) and Richard Friar (right) showed attendees some equipment at the new facility.

An Eye on TRI: Lee Leichter, P/L Biomedical

Lee Leichter has over 35 years of experience in the healthcare industry. For the last 15 years he has concentrated on providing direct, hands-on assistance to domestic and international pharmaceutical, biotechnology and medical device companies as a consultant. He works primarily with companies marketing drug delivery and combination products in the United States, Europe and Canada.

Last year, the U.S. FDA's rule requiring combination products to be in compliance with 21 CFR 4 became effective. How does your course address this new rule?

First, it is important to point out that although the new rule only became effective last year, it remains FDA's position that companies who manufacture combination products have always been required to meet *all* of the GMP requirements applicable to the constituent parts of their product. They stress that this regulation does not define any *new* GMP requirements, only identifies a "streamlined" way of complying.

Even so, the regulation provides significant insight into FDA's thinking, mostly in the preamble where they address comments received on the draft rule. The course will dedicate a significant amount of time providing insight into how this new rule impacts existing, as well as new, drug delivery combination products, including strategies for compliance. FDA has promised publication of an accompanying guidance to the regulation that will address many of the remaining questions and issues. If the guidance is published before the course, it will be included in the curriculum.

Can you tell us more about the course? Who do you recommend attend it?

In addition to U.S. GMPs discussed above, the course will touch on the EU's quality system requirements, and strategies and potential to leverage the systems implemented at your device partner's facility. But first, the course will start out with a history of combination product regulations, the application of regulations and directives to drug delivery, the differences in U.S. and EU requirements and some regulatory strategies. The balance of the course will address the technical requirements, including functional aspects,

Continued at bottom of page 13

Lee Leichter will serve as the instructor for the one-day course, "Technical and Regulatory Challenges of Drug Delivery Combination Products – Prefilled Syringes, Autoinjectors and Injection Pens" held on Oct. 9 from 8:30 a.m. to 4 p.m. For more information, please visit www.pda.org/pfscourses2014.

TOOLS FOR SUCCESS

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

Leverage Volunteer Experience to Achieve Career Success

Rebecca Stauffer, PDA

MANY of us face a common conundrum when changing careers or seeking a new internal role at the same company: how to demonstrate years of experience in, say, Development, when you've spent the last ten in Manufacturing Operations?

For PDA board member **Ursula Busse**, moving into a new role within Novartis involved leveraging her broad volunteer history with PDA.

"What led to my promotion is not an extensive experience in quality assurance," she explained. "I was promoted to my current role because I kept myself informed about the changes in regulations and the global regulatory trends through my activities at PDA."

In October 2013, Busse became Head of GxP Regulations Coordination, following five years in technical operations as Head of the Project Office for Novartis' biopharmaceutical operations. In her new role, she is responsible for monitoring changes in global regulations and their impact on the company's quality system. She also handles external relations for the quality group by getting her company involved in outside activities that affect the quality/technical space.

Not surprisingly, this new role required her to be familiar with hot regulatory topics.

"I stayed informed on current topics—on trends, on updates, on discussions—through my participation in PDA task forces, planning committees, attending PDA meetings, and so on," Busse said.

Her volunteer work at PDA includes serving as a member of several conference planning committees, task force involvement and, of course, her election to the board.

So, how can a PDA volunteer move up the ranks?

"An important aspect is to get known or to have some visibility, because leaders are assigned by other people recognizing them for their leadership capacities," Busse emphasized. "If you're a good leader but you stay invisible, you will not move up to leadership roles. So, I would encourage new members or volunteers who would like to move into leadership roles to get involved in activities where they can show that they have the ability to lead."

Her recommendations include starting as a member of a planning committee for a conference, joining an interest group, and serving on a task force. Pick up small tasks and work up from there. But, most importantly, engage in roles that one enjoys.

"If you're good, then people will ask you to do more," she said.

But don't forget to be visible within your own companies, Busse added.

"It's always good to build networks," she said, "to get connected to people whether it's within companies or outside, via PDA, for example. PDA is a wonderful opportunity to get connected with people in other companies, connected to regulators, whether it's in formal exchanges and meetings or informal discussions in the networking events."

In addition, she recommended participating in company-wide initiatives even if they appear to have little benefit to you personally because it's a great way to make connections within your company.

Another key factor is to always keep learning.

"In today's world, science is advancing at a fast pace, and new concepts such as QbD and risk management approaches and knowledge management are becoming part of our daily operations—these ask for people who have cross-functional experience, so I would encourage people to gain work experience in several different areas. For example, someone who

started out in Technical might gain experience in Development and then Manufacturing, then move over to quality—maybe work some time in Regulatory, I think that's needed today to move on to leadership roles," Busse concluded.

Varied experiences and an extensive network enabled her to achieve career success. Membership in associations like PDA can allow you to gain the knowledge and ability to build a network. Although you might be happy in your current role, it wouldn't hurt to consider your next role and the steps you need to take to get there.

Ursula's Timeline

Career Highlights

- **October 2013** – Head GxP Regulations Coordination
- Head of Project Office, Novartis
- Regulatory CMC Liaison III, Novartis
- Director, Quality Assurance and Regulatory Affairs, Medicago
- Assistant to the Scientific Director, Medicago
- Begins career at DiagnoCure

PDA Volunteer Highlights

- Co-chair of the PDA Annual Meeting Planning Committee and mAb workshop
- Member of the Awards Committee
- mAb workshop chair
- Annual Meeting Planning Committee member
- PCMO℠ Capture Knowledge Management Task Force
- Involved with PDA Canadian Chapter
- Elected to the PDA Board of Directors

Eye on TRI continued from page 11

material stability, usability and risk management and the current clinical expectations and strategies for clinical bridging.

The course will be of value primarily to professionals in research (device development), regulatory affairs, quality assurance, compliance and quality engineering in the pharmaceutical industry as well as representatives from drug delivery device companies interested in understanding and supporting their customer's needs. It will, however, be of interest to anyone who would like to learn about this exciting area.

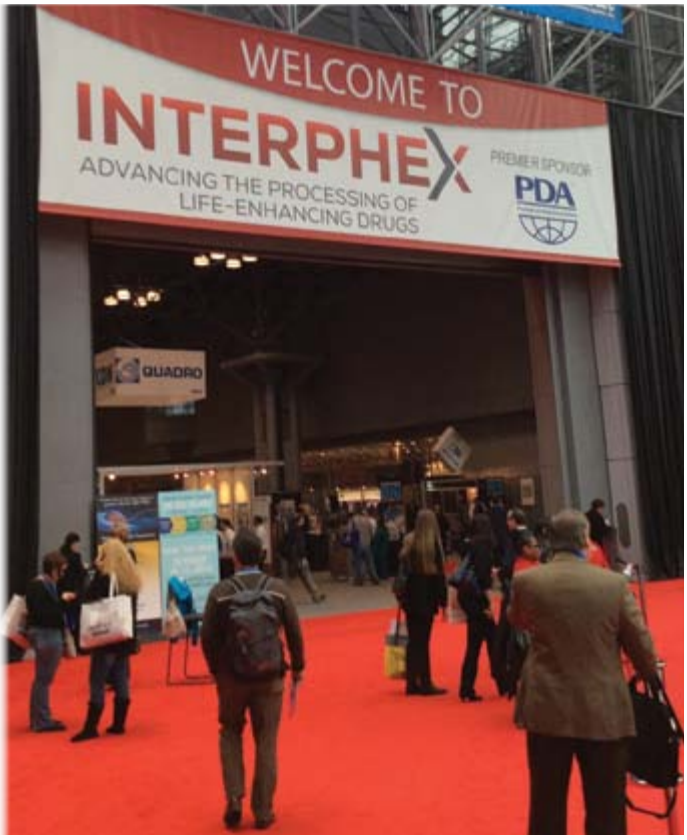
You will be offering the course at the upcoming *2014 PDA Universe of Prefilled Syringes and Injection Devices* conference. I understand that as Leader of the U.S. Combination Product Interest Group, you will help organize a combination products workshop held in conjunction with this conference. Can you describe your vision for this workshop?

The workshop is intended to provide the attendees examples of real-life experiences from their peers detailing the challenges they faced during development, approval and manufacturing of their drug delivery combination products. These presentations will likely focus on one element of their activities (e.g., verification and validation, regulatory inspection and compliance, clinical studies, etc.), providing the activities and the results, both positive and negative. It is also planned to have the speaker participate in panel discussions discussing what has succeeded, what is likely to no longer work and what strategies are most likely to succeed in the future.

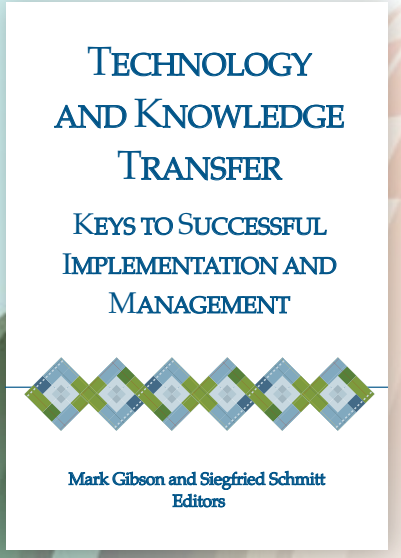
Interphex

March 18–20 | New York, NY

PDA served as a Premier Sponsor for this year's INTERPHEX show in New York, offering members attending the meeting access to an exclusive members-only lounge.



New Release at the PDA Bookstore



Item No. 17318

Technology and Knowledge Transfer: Keys to Successful Implementation and Management

Edited by Mark Gibson and Siegfried Schmitt

Written by global subject matter experts, this book offers the practical experience needed to obtain a competitive edge. The successful technology transfer from research and development to the commercial production site is a critical process in the development and launch of a new medicinal product. An unsuccessful transfer can result in possible launch delays and lost sales as well as require increased resources, time and money to make corrective actions. This book will help companies take a proactive approach to streamlining and optimizing their technology transfer processes to ensure success. Highlights of the text include:

- Regulatory and Business Perspectives
- Strategies and Planning
- Drug Substance Development and Technology Transfer
- Chemical as well as Biopharmaceutical Drug Product Development
- Analytical Methods
- Transfer of Bioassay Methods
- Outsourced Activities management
- Audits and Inspections
- Training

go.pda.org/TAKT

ABOUT THE EDITORS

MARK GIBSON, BPharm, PhD, CChem, MRSC, MRPharmS, is currently an Independent Consultant to the Pharmaceutical Industry. His experience encompasses 30 years working in the pharmaceutical industry, both as a bench scientist and a manager, in the development of new chemical entities and line extensions for American Cyanamid (Lederle), Fisons Pharmaceuticals, Astra Pharmaceuticals and AstraZeneca.

SIEGFRIED SCHMITT, PhD MSc CSci CChem FRSC, is a Principal Consultant with PAREXEL Consulting, which he joined in 2007. He started his career in 1989 with Roche in Basel, Switzerland, where he worked as Senior Production Chemist. This was followed by positions with Raytheon as Validation Manager, ABB as Senior Lead Consultant and GE Healthcare as global Quality Director, before joining PAREXEL.

snapshot

PDA Surveys the Process Validation Landscape

Jahanvi (Janie) Miller, PDA

In October 2012, PDA commented on the EMA draft guidance, *Guideline on Process Validation* (EMA/CHMP/CVMP/QWP/70278/2012-Rev1). Then, in 2013, PDA published *Technical Report No. 60: Process Validation: A Lifecycle Approach*, as part of the Paradigm Change in Manufacturing Operations (PCMO[SM]) initiative. TR-60 reviewed requirements for process validation studies across the three-stage approach defined by the U.S. FDA, while taking into consideration the comments submitted on the EMA draft guidance, and presented best practices for integration with supporting quality systems. TR-60 also covers both traditional and nontraditional (enhanced) process validation terminology as employed by EMA. In this context, nontraditional or enhanced validation may use continuous process verification (CPV) as an alternative approach to traditional process validation.

To gauge industry response to the earlier 2011 FDA Guidance, *Process Validation: General Principles and Practices,* and the challenges associated with process validation, PDA conducted the *2014 PDA Process Validation Survey*. This survey was distributed to the Process Validation Interest Group, those involved in the development and review of TR-60, reviewers of the FDA draft guidance, and any other parties interested in participating.

The survey is expected to reveal how companies are implementing the new lifecycle approach to process validation. Preliminary results from the survey were presented at the *2014 PDA Annual Meeting* in San Antonio, Texas, during the Process Validation Interest Group session.

Preliminary results from the survey show that the majority of respondents define process validation within their companies according to the three stages of process validation. An overwhelming majority of respondents also use prior knowledge from similar processes to support process characterization or process design studies. The majority also use the same process validation number of batches across the globe.

The survey results will eventually be available for sale at the PDA Bookstore (www.pda.org/bookstore).

PDA Journal *Top 10*

Viral Safety and PQRI Draw High Readership Levels

Below are the top ten articles from the *PDA Journal of Pharmaceutical Science and Technology* read during the month of March:

1. PQRI Special Section – *Review*
Diane Paskiet, et al. "The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP)" September/October 2013

2. Technology/Application
Cliff Campbell, "FDA 2011 Process Validation Guidance: Lifecycle Compliance Model" March/April 2014

3. PQRI Special Section – *Research*
Dennis Jenke, et al. "Extractables Characterization for Five Materials of Construction Representative of Packaging Systems Used for Parenteral and Ophthalmic Drug Products" September/October 2013

4. Conference Proceeding – *Introduction*
Lixin Xu, et al. "Role of Risk Assessments in Viral Safety: An FDA Perspective" January/February 2014

5. Conference Proceeding – *Article*
George Miesegaes "Viral Clearance by Traditional Operations With Significant Knowledge Gaps (Session II): Cation Exchange Chromatography (CEX) and Detergent Inactivation" January/February 2014

6. Review
Fatima Hasanain, Katharina Guenther, Wayne M. Mullett, and Emily Craven "Gamma Sterilization of Pharmaceuticals—A Review of the Irradiation of Excipients, Active Pharmaceutical Ingredients, and Final Drug Product Formulations" March/April 2014

7. Technology/Applications
T. Eaton, C. Wardle, and W. Whyte "Use of a Real-Time Microbial Air Sampler for Operational Cleanroom Monitoring" March/April 2014

8. Conference Proceeding – *Introduction*
Kurt Brorson "Overview of 2009 Indianapolis Conference White Paper: The Goal of an Integrated Viral Clearance Strategy" January/February 2014

9. Conference Proceeding – *Introduction*
Johannes Blümel "Viral Safety Perspective from the Paul-Ehrlich-Institut in Europe" January/February 2014

10. Research
Wendy Shieu "Filling of High-Concentration Monoclonal Antibody Formulations into Pre-Filled Syringes: Filling Parameter Investigation and Optimization" March/April 2014

Members can access journal content from the past two years for free at journal.pda.org.

Tech *Trends*

Rampant Counterfeiting Demands Cutting-Edge Solutions

David Wicker, Document Security Systems

According to the World Health Organization (WHO), the range of counterfeit pharmaceutical products reaching markets around the world continues to broaden with increasing internet retail sales for both branded and generic drugs ***(1).*** In more than 50% of cases, medicines purchased over the internet from illegal sites have been found to be counterfeit. That same study states that worldwide counterfeit drugs sales were estimated to top U.S. $75 billion—a 90% increase over the previous five years.

While there are many statistics on counterfeiting's impact on companies and consumers, these studies only give a glimpse into the extent of the problem. Most experts believe that the increasing sophistication of counterfeits along with flexibility from the internet to market them, has led to increasing occurrences of counterfeits entering the supply chain.

Because imaging technology evolves so rapidly and online retail stores can quickly disappear and reappear elsewhere, the digital security and authentication business must work hard to remain ahead of counterfeiters. One of the biggest challenges involves staying ahead with innovation and technology.

The technologies fit into two categories: anticounterfeiting and authentication. Anticounterfeiting technologies make it difficult for counterfeiters to accurately reproduce a document, label or package with a desktop scanner or a copier. Authentication technologies provide validation of genuine articles or websites through proprietary lenses, optically variable changes and even through leading edge smartphone applications.

For the pharmaceutical industry, authentication features need to resist duplication, provide real-time authentication with devices that are not cost prohibitive and are readily available, and can report problems within the supply chain. Solutions should also secure, organize and archive the collected data for brand owner and investigator use. Optimal authentication features will also help consumers determine if they are purchasing from an authorized website.

[Editor's Note: Get more information on this topic at the *2014 PDA/FDA Pharmaceutical Supply Chain Conference.* See article on page 39 for more details.**]**

Reference

1. Growing threat from counterfeit medicines. *Bulletin of the World Health Organization,* 2010, 88: 247–248 www.who.int/bulletin/volumes/88/4/10-020410/en/

About the Author

David Wicker, Vice President of Research and Development, DSS, Inc. has over 24 years in the industry specializing in developing optical deterrents and authentication using AuthentiGuard technology.

Task Force *Corner*

Task Force Helps Smooth Path for GCBT Products

Joshua Eaton, PDA

The age of gene and cell-based therapies (GCBTs) is slow to arrive, but gaining momentum. Notably, these technologies are progressively being approved in Europe. Provenge (for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer) is the fourth advanced therapy medicinal product (ATMP) to be recommended for marketing authorization by the CHMP since the legislation on advanced therapies became operational. The other three therapies are Glybera (for the treatment of lipoprotein lipase deficiency and the first gene therapy authorized in Europe) and the tissue engineered products for remediation of damaged cartilage, ChondroCelect and MACI.

PDA members are working to address some of the issues associated with GCBTs, including manufacturing challenges and phase appropriate implementation of GMPs, commercial production and related production method decisions, and the inherent variability of the end product. The challenges are many and the points to be addressed can become overwhelming.

As a first step in smoothing the path to GCBT development, the PDA Gene and Cell-Based Therapies task force has continued their effort to present coherent control strategies for the manufacture of autologous cell-based therapies. **Michele Myers** of GSK and **Valerie Pimpaneau** of Voisin Consulting, are leading subgroups to tackle the issues of defining quality target product profiles (QTPPs) and critical quality attributes (CQAs) along with evaluating critical process parameters (CPPs) and raw materials qualification. This will be the first in a series of technical reports to address these complex and quickly evolving products and their associated production, quality and safety concerns. The internationally based members of the team have joined with participants from some European regulatory agencies to foster a harmonized vision of the GCBT arena.

The task force will convene again at the next PDA Europe *Advanced Therapy Medicinal Products* (ATMP) conference. This will be the fourth ATMP conference and will be held June 3–4 in Madrid, Spain (see p. 20 for more details about the conference). Organized in close cooperation with European regulators in this field, the program's focus will be on CMC development topics in early and late stage development and will also present new technical developments in the field.

[Editor's Note: See the Nov/Dec *PDA Letter,* p. 28, for a report from the 2013 ATMP conference.]

Demystifying Pharmaceutical Microbiology

Renee Blosser, U.S. FDA, and Program Committee Member

Can your company identify current trends in environmental monitoring? Can it summarize the latest advances in rapid microbiological methods, microbial identification, endotoxin testing and the use of statistics for data review and validation? Can it describe the role of microbiology in QbD, including management of microbial risks, contamination control and risk management in aseptic processing?

The underlying science of microbiology can be mystifying for many. Yet awareness of the latest developments and trends in microbiology presents an opportunity to see solutions to problems that plague our industry on a daily basis.

For this reason, PDA is excited to announce the *9th Annual Global Conference on Pharmaceutical Microbiology*. Presentations will explore current issues in sterile manufacturing, innovative technologies, parametric release, workforce development, and a variety of other topics that highlight the ever-evolving world of pharmaceutical microbiology.

Following the conference, on October 23–24, PDA TRI will offer four courses covering regulations governing nonsterile environments, environmental compliance, objectionable microorganisms and microbiological risk assessments. For more information on these courses, please visit www.pda.org/microcourses2014.

The first two days of the conference will include two keynote addresses, various plenary and breakout sessions, and poster sessions. One exciting keynote session will honor the golden anniversary of the limulus amoebocyte lysate (LAL) test and provide insight into the advances in LAL testing from past through present. The second keynote session will examine recent outbreaks of norovirus on cruise ships and methods for adequate disinfection. Other popular sessions will return with new presentations including "Urban Myths" and "Emerging Leaders."

9th Annual Global Conference on Pharmaceutical Microbiology • Bethesda, Md. • Oct. 20–24 • www.pda.org/microbiology2014

The final day of the conference will focus on standards and regulation. The "USP Updates" session will provide an overview of the proposed changes to USP general chapters related to microbiology. A U.S. FDA regulator will give a presentation on global and domestic inspectional issues, which may include case studies. The conference will close with the "Ask the Regulators" panel discussion giving attendees an opportunity to pose questions directly to FDA personnel with expertise in field and center regulatory issues.

Advance Your Device Knowledge at This Year's Prefilled Meeting

David Haase, Genentech, and Program Committee Member

2014 PDA Universe of Prefilled Syringes and Injection Devices • Huntington, Calif. • Oct. 6–10 • www.pda.org/prefilled2014

Have you noticed that terms like "patient centric design," "human factors," and "patient outcomes" are becoming the hot topics of the day in our device world? Do you know how to incorporate that kind of thinking into your development projects? Have you been able to keep up with all the new technologies entering this marketplace?

The device world is ever changing, especially now more than ever. If you're like me, you're always reading about the latest trends in various industry publications, looking up case studies in trade and academic journals and reaching out to leading experts for more information.

PDA TRI is hosting four courses to complement what you learned at the conference from with "Prefilled Syringe User Requirements," "Syringes and Elastomers: Understanding the Effects on Quality and Demonstrating the Production Process, Influences and Needs," and "Technical and Regulatory Challenges of Drug Delivery Combination Products – Prefilled Syringes, Autoinjectors and Injection Pens" on Oct. 9 and "Risk Management for Temperature Controlled Distribution" on Oct. 10. For more information, please visit www.pda.org/pfscourses2014.

What I love about PDA's annual *Universe of Prefilled Syringes and Injection Device* meeting is that you can hear about all the latest topics from industry experts and mingle with nearly a thousand delegates.

Come learn about the latest developments in large volume bolus injectors. Discover the best approach to incorporating human factors into your device design. Find out if plastic syringes are progressing toward the market. Learn how you might help improve patient adherence and compliance through your product design and training.

So don't miss the biggest and best conference of the year dedicated to injection devices and combination products. Make your plans to come to the meeting and be amazed at how much you can learn and take back to your job.

New Therapies Offer Novel Treatment Options

Program Planning Committee Co-chair Wilfried Dalemans, Tigenix

Advanced Therapy Medicinal Products (ATMP) is a summary name for a class of relatively new therapies based on cell, gene or tissue engineered products. Apart from being different in composition from the classical medicinal products, they also represent an alternative type of therapeutic action. Indeed, rather than exerting their therapeutic action by specifically binding a target molecule, neutralizing a given protein target (by monoclonal antibodies) or providing a missing protein, they directly aim to address the cause of the disease rather than targeting or alleviating the symptoms. ATMPs act mainly by replacing, repairing, or regeneration mechanisms, either at the level of the cells, tissues or organs, or by correcting genetic deficiencies in the body's cells. As such, they open new avenues of treating patients in a fundamental and durable manner.

Examples of ATMPs are gene therapy for haemophilia, cell therapy for cartilage repair or cancer treatment, or trachea transplantation by a specifically designed tissue engineered product. These novel types of medicinal products thereby open promising options to treat patients with current unmet medical needs or where classical drugs would not be applicable.

The first PDA Europe activities in the ATMP field started in 2007 and resulted in a yearly conference, which is now being held for the fourth time, organized in close cooperation with European regulators in this field. As ATMPs are of a high complexity in composition and use, there is a clear need to discuss the challenges in product development and in nonclinical and clinical testing. Since the first products have now also obtained regulatory approval, commercial and postmarketing experiences have become available.

Advanced Therapy Medicinal Products • Madrid, Spain • June 3–4 • https://europe.pda.org/atmp2014

This year's program will specifically focus on CMC development topics both in early and late development as well as to illustrate new technical developments in the field. Selected keynote lectures and a series of case studies encompassing a broad range of product types and development approaches will illustrate how ATMPs are currently being developed and tested.

The 2014 PDA *Advanced Therapy Medicinal Products* conference in Madrid, Spain, will once again provide a unique interactive discussion forum and opportunity for exchange of information allowing participants to reflect on and discuss the different perspectives and areas of expertise.

Protect Your Biologics from Virus/TSE Threats

Albrecht Gröner, PhD, CSL Behring

Pathogen safety is an inherent issue of biologicals and biopharmaceuticals. There is a possibility that emerging pathogens potentially could contaminate the starting material plasma used for the production of plasma-derived products. Or raw materials used for the expansion and maintenance of cell cultures for the production of biopharmaceuticals or advanced therapies could be contaminated. Emerging concerns include the use of "research grade" animal-derived reagents to generate or clone cell lines expressing desired proteins, effectiveness of "barriers" around fermenters to prevent virus contamination of cells, and hepatitis E virus (HEV), a virus now in the focus of stakeholders of plasma-derived products. Risk mitigation strategies are key for biopharmaceuticals, and congruent methods for virus reduction are employed during the production of plasma-derived products. All are used to minimise such virus contamination risk and protect patients from supply issues and potential infections. Furthermore, the contamination of biologicals/biopharmaceuticals by Transmissible Spongiform Encephalopathy (TSE) agents is still a risk.

2014 PDA/FDA Virus & TSE Safety Conference • Bethesda, Md. • June 9–13 • www.pda.org/virus2014

PDA will sponsor its 8th *Virus & TSE Safety Conference* continuing a more than ten year tradition covering the broad area of pathogen safety issues. This year's conference offers expert overviews on many subjects, and will be an opportunity for dialogue and sharing experiences between industry—manufacturers of biotherapies/contract research organizations—and health authority representatives during the dedicated Q&A time slots, in panel discussions and poster sessions.

The PDA Virus & TSE Safety Course Series will take place on June 12–13 with two courses. The "Virus Contamination in Biomanufacturing: Risk Mitigation, Preparedness and Response" course will take place on June 12, while on June 13 the "Introduction to Emerging Methods for Virus Detection" will occur. For more information and to register, visit www.pda.org/viruscourses2014.

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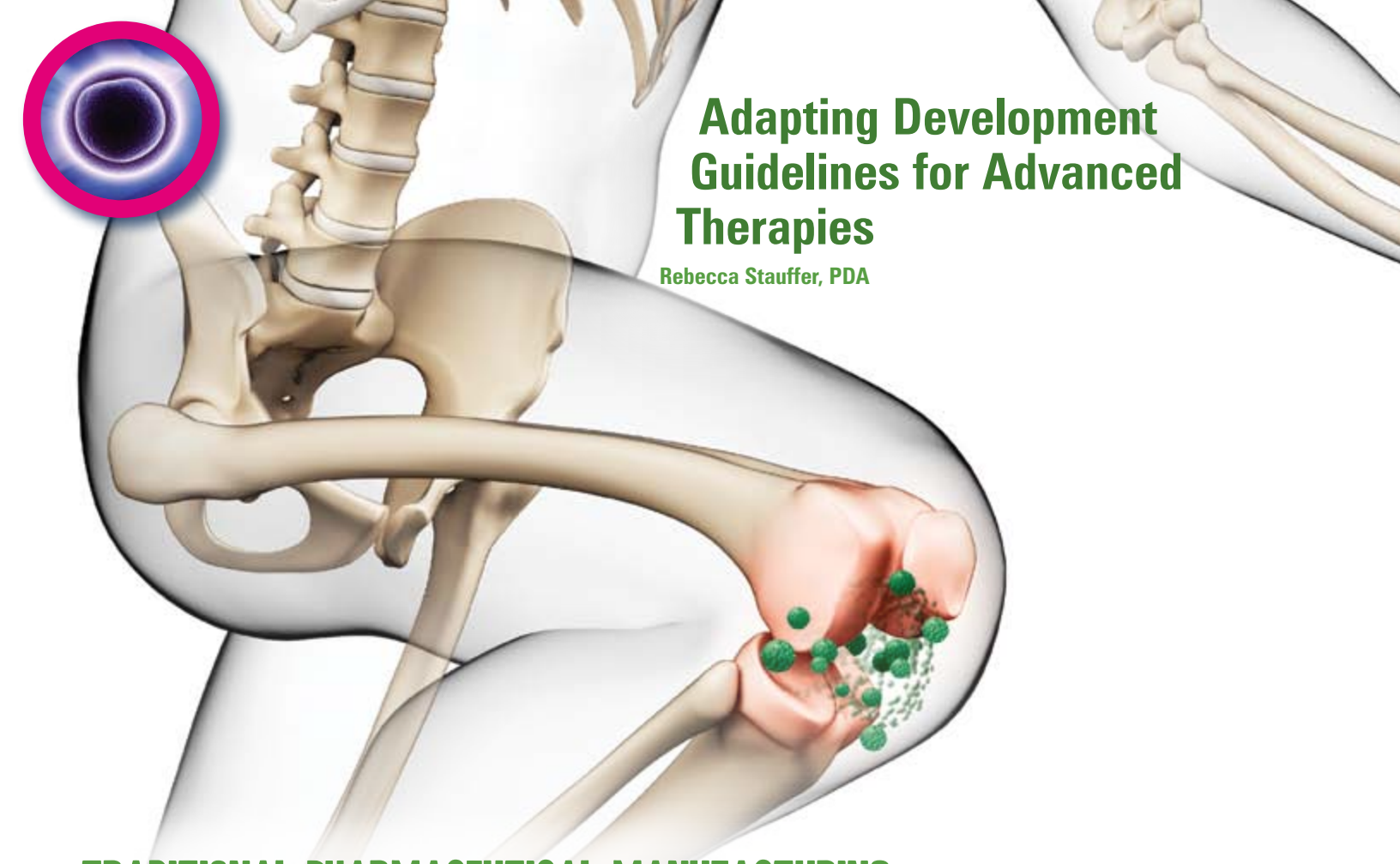

Adapting Development Guidelines for Advanced Therapies

Rebecca Stauffer, PDA

TRADITIONAL PHARMACEUTICAL MANUFACTURING is very familiar to all of us. It is easy to picture the conventional setup whereby a company maintains a facility involving large batch manufacturing in an assembly line fashion, manages extensive supply chains and creates product with lengthy shelf lives.

The picture for advanced therapy products is much different, emphasized **Wilfried Dalemans,** PhD, Chief Technical Officer, Tigenix, during his presentation at the *2014 PDA Annual Meeting* ***(1).***

"It's not like pills or small biological molecules where the processes are well established," he said. "When you are in the cell therapy world, your manufacturing [environment] looks more like a cell culture lab than a high tech manufacturing facility. So, it makes the approach quite different from the classical approach."

Tigenix is a small Belgium-based biotech company founded in 2000. A few years ago, the company developed ChondroCelect, a cell-based medicinal product comprised of autologous cartilage cells. The product is used to repair knee cartilage defects in adults. This was the first cell therapy product to receive approval from the EMA. Production begins with a biopsy of the patient to extract cells. These cells are then manufactured in a controlled environment before being administered to the patient.

The company also has another product—Cx601, a stem cell therapy—that is in Phase III development. This therapy would treat patients' fistulas from Crohn's disease. Two other stem cell treatments would treat autoimmune disorders.

Dalemans focused his talk on the company's ChondroCelect product.

"First of all, cells have a very complex composition," he said. "Very important also, its living material so all kinds of biochemical processes can take place in your product. And of course, everyone who works with cells knows they're very fragile."

This means traditional purification or sterilization methods cannot be used.

"On top of this, these products have a very short shelf life," Dalemans emphasized.

Cell Variabilities Present Further Challenges

During development, process validation of autologous material proved to be a challenge due to the fact that each product was essentially different. Autologous cells are extracted and then reinserted into the same donor as opposed to allogeneic cells which are extracted from individuals other than the recipient. These autologous cells are unique to each individual patient, and thus possibly have

Article at a Glance

- 48-hour shelf life presents sterility, supply chain challenges
- Despite the small scale of manufacturing, quality remains key
- Tigenix trains the orthopedic surgeons responsible for injecting the product into patients

different baselines for each patient. In response, his company chose to conduct a splitted biopsy sample approach together with parallel runs of individual biopsies for defining critical parameters.

"This gave us quite a comprehensive data package, despite the individual variability of the cells," he said.

For the selection of critical quality attributes (CQAs), he explained that his team relied on their knowledge of cell biology, since most have worked closely with cells for a long time and they "know what the key quality parameters of your cells are."

His group enlisted many different biological tests relevant for chondrocytes and each of them pointed in the same direction, indicative of thorough quality processes. He also pointed out that for complex products like cells, it's important to not focus solely on one critical attribute but instead combine several of them.

"In addition, since many of the tests are biological assays, assay development and validation is also a challenging step," he added.

Dalemans then described extensive product characterization as one of "the holy grails of cell therapy." Ultimately, the company wanted the product to be used to regenerate healthy cartilage—creating high quality cartilage in patients. To achieve this potency target, his company looked at *in vivo* models, culture assays at the cellular level and marker analysis at the molecular level.

Short Shelf Lives, Sterility Testing are Poor Match

"Another important point is sterility testing," he said.

This proved to be a challenge due to the 48-hour shelf life of the product, especially when it came to meeting the sterility requirements of the European Pharmacopoeia. After speaking with regulatory authorities, his team chose to develop the product in an aseptic process while conducting multiple testing ("intermediate sterility testings") during manufacturing and anticipating final release testing by conducting a sterility test very close to the end of product formulation just before it is administered to the patient.

Education even in the administration of cells is very important as well

His team still conducts the compendial sterility test, but data becomes available only 14 days after product release and administration the patient.

In speaking to the *PDA Letter* following his presentation, Dalemans expanded on the challenges with sterility testing: "We have been thinking about using rapid sterility testing but you still need to perform a culture step for a certain amount of time, ranging between four to seven days. It thus still takes you beyond the end of the shelf life, so, yes, you have your results more rapidly but it's not yet that rapid that you could say 'I can release my product on the real data of the sterility test.' It is improving but it is not solving the problem at this stage."

His company, however, is looking further into newer tests under development.

"We have for instance been looking to a technology that looks directly into the cell suspension to see if bacteria are present, but results showed that this can only be done with quite clear solutions. When you have a cell suspension that's loaded with cells and other molecules, there's too much interference."

The intermediate sterility tests Tigenix uses are, at the moment, the most suited method for ensuring the safety of the product because "having multiple sterility checkpoints together with a sterility test two or three days before the product is shipped, could eventually have major contamination issues already detected, and so feel comfortable that the sterility of the product is ensured."

Dalemans also added that "at the end of the day, your sterility test is only a test. Having the sterility done is in your methods and your process, so the focus on the process verification and media fill is really where you try to guarantee at best your sterility."

Cell Manufacturing Considerations

In his presentation, Dalemans also delved into the variety of logistical challenges presented by short shelf life with temperature sensitivity.

"With this short shelf life there is also highly managed logistics," he said. These cells require specific temperatures. In addition, care has to be taken to avoid being irradiated if the cells are transported through an airport. This requires closely coordinating with the logistics provider.

"Also, an important point is manufacturing standardization," Dalemans said. His team takes a lead role in training the surgeons removing the cells from patients as "they play a key role in extracting the starting material," which needs to comprise high-quality cells.

Before concluding his talk, Dalemans explored some of the unique GMP aspects of producing cell therapies.

"Each batch is one product which means you're working on a small scale," he said. The development process is even more unique as you can have operators conducting many operations in parallel. But regulators want to see a quality-driven process even though each batch is different.

"So, it's very important that you take into account that there is good separation of the individual biopsies," Dalemans said. In addition, each batch will feature cells with different rates of growth, so, "when you're planning, you need to take this into account."

Due to the parallel production of different cell lines specific to individual patients, prevention of cross contamination is very critical and it's important to have good line clearance.

In the Q&A following his talk, Dalemans went into greater detail regarding the Phase III development process, describing how extensive analysis of patient data plus product characterization allowed him to differentiate his product from other available therapies in discussions with regulators. ➤

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20-21
2014 PDA Packaging Conference
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www.pda.org/packaging2014

21-22
2014 PDA Knowledge Management Workshop – Enabler for ICH Q8-Q11, WRM and Continued Process Verification Course Series
Bethesda, Maryland
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22-23
2014 PDA Packaging Course Series
Washington, DC
www.pda.org/packagingcourses2014

JUNE EVENTS

2-6 and 23-27
2014 Aseptic Processing Training Program – Session 3
Bethesda, Maryland
www.pda.org/2014aseptic3

2
Manufacturing and Testing Challenges of ATMPs
Madrid, Spain
https://europe.pda.org/WSATMPs2014

3-4
Advanced Therapy Medicinal Products
Madrid, Spain
https://europe.pda.org/ATMP2014

3-5
2014 PDA/FDA Pharmaceutical Supply Chain Conference
Washington, DC
www.pda.org/supplychain2014

5-6
2014 PDA/FDA Pharmaceutical Supply Chain Course Series
Washington, DC
www.pda.org/supplychaincourses2014

5-6
Environmental Monitoring
Madrid, Spain
https://europe.pda.org/TCEnviMon

5
PDA Ireland Chapter Meeting on Visual Inspection
Dublin, Ireland
https://europe.pda.org/IRVisInsp2014

9-11
2014 PDA/FDA Virus & TSE Safety Conference
Bethesda, Maryland
www.pda.org/virus2014

12-13
2014 PDA/FDA Virus & TSE Safety Course Series
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17-18
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www.pda.org/aseptic2014

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JULY EVENTS

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26
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26
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26
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Until recently there was less clarity on the regulation of these types of products in Europe compared to the United States

An audience member asked how the company ensures that cells extracted from a healthy patient do not lead to mutagenicity. Dalemans' explained that the conditions his company's cells are grown in use such a short time frame that potential mutagens are unable to grow during that time. His team also conducts expansion tests and other studies to address potential mutagenicity.

Additionally, Tigenix follows up with patients receiving ChondroCelect for five years to ensure the long-term health of patients.

Doctors Need Training Too!

Following the session, the *PDA Letter* asked Dalemans if he could describe differences between the U.S. and EU markets for advanced therapies. He said he does not see much variation, however, he noted that until recently there was less clarity on the regulation of these types of products in Europe compared to the United States. In the latter, these products fell under the BLA system and the U.S. FDA also issued a guidance for these products early on.

He also believed that the U.S. marketplace is perfectly conducive to the development of advanced cell and gene therapies, and pointed to the number of successful companies currently developing such products in the United States. In fact, he added, his company has no plans to market ChondroCelect in the United States because a similar product is already under development by a U.S. company.

Dalemans also provided additional insight into Tigenix's role in training the surgeons who initially extract the cells from the patient. While medical doctors in certain specialties such as oncology regularly perform biopsies, the doctors extracting cells for the ChondroCelect product are orthopedic surgeons, who do not routinely conduct biopsies.

"When you put it into the orthopedic world, there is not much, let's say, routine applications where you would take biopsies," Dalemans explained. Depending on the product, his company works with surgeons in a variety of specialties.

"We have a program with stem cells running for Crohn's disease, there we work with surgeons who do gastrointestinal surgery, so we really work with specific classes of surgeons who are used to working with the region where the cells have to go. In a lot of these applications, they are not used to taking biopsies," he said.

The company did not immediately plan to train the doctors, but soon found out the hard way. Prior to careful training, the orthopedic surgeons compromised the quality of the starting material by biopsying cells while cleaning patient's lesions.

"Well, you should realize this material that comes out of the lesion is inflamed and so on, and this is not the best material," Dalemans explained. Orthopedic surgeons are not as familiar with extracting high quality cell material since they "don't think that way."

"You need to educate them. Say, 'listen, if you want us to produce this in a decent amount of time with good cells, please provide us with a decent amount of starting cells, otherwise it will take five months before we can grow enough cells.' So that's the education.

"Education even in the administration of cells is very important as well," he said, citing cases where surgeons have taken frozen cell therapy products and put them in microwave ovens to warm up; room temperature is the only way to prepare the products for administration.

Adapt the Rules for Future Medicines

While it can be challenging to follow CMC guidelines for manufacturing cell therapies, Dalemans recommended that companies involved in this area look at it as taking the CMC rules used for traditional products and then "translating" these rules to suit development of cell therapies.

Personalized medicines and other ATMPs present the future of drug development so this will mean working closely with regulatory authorities and close collaboration within industry to tackle these challenges.

Reference

1. Dalemans, W. "Cell and Gene Therapy." Presented at the 2014 PDA Annual Meeting, San Antonio, TX, April 2014.

About the Expert

Wilfried Dalemans is Chief Technical Officer at TiGenix, Belgium. He is responsible for the global technical operations of the company, encompassing coordination of product development and lifecycle in R&D and Industrialization, and overseeing the clinical and commercial manufacturing operations of the company.

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Developing an Effective Manufacturing Control Strategy for Cellular Therapy Products

Jean Stanton, Johnson & Johnson

Successful commercialization of a cellular therapy product requires the development of the best quality product to suit patient needs. In the pharmaceutical industry, it is generally accepted that quality can no longer be tested or inspected into a finished product, but rather quality, safety and effectiveness must be "designed" and built into a product and its manufacturing process. The concept of QbD provides a systematic approach that begins with predefined objectives, and emphasizes product and process understanding, and process control based on sound science and quality risk management ***(1).*** It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives as well as ensuring consistent process performance. Developers of cellular therapy products can use specific aspects of QbD to develop an effective manufacturing control strategy. These aspects include: the quality target product profile (QTPP), critical quality attributes (CQA), critical process parameters (CPP) and critical material attributes (CMA). Successfully applied, they can lead to reduced product and process variability, reduced development costs, and faster time to market.

With this in mind, I would like to offer one perspective into the development of such a control strategy, including what must be achieved to reach the desired end, offer examples of specific tools which can be used to identify the CQAs, CPPs, and CMAs, and control choices made during the development of a control strategy. I will present this perspective at the upcoming *Advanced Therapy Medicinal Products* conference ***(2)***.

QbD is a concept that was first outlined by quality expert **Joseph M. Juran**, most notably *Juran on Quality by Design* ***(3).*** Juran believed that quality could be planned, and that most quality crises and problems relate to the way in which quality was planned. These principles have been used to advance product and process quality in almost every industry, particularly the automotive industry, and they have been adopted by the pharmaceutical industry as a vehicle for the transformation of how drugs are discovered, developed and commercially manufactured. The traditional approach to product development and manufacture often involved the use of empirical methods to relate process to product and the product to the clinic. The QbD approach is defined in ICH Q8 guideline as a "systematic approach to develop-

ment that begins with predefined objective and emphasizes product and process understanding and process control" ***(4).***

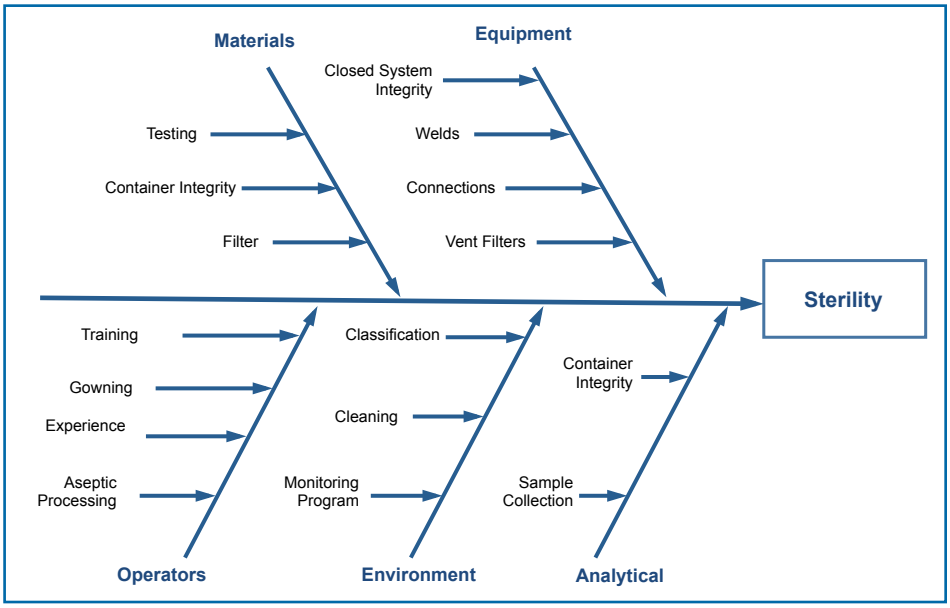
In my presentation, each aspect of QbD is discussed in more detail with examples to highlight how they can work in the development of an allogeneic cell therapy product. I start with the development of the QTPP—the quality characteristics that a product should possess in order to reproducibly deliver the therapeutic benefit promised on a product label taking into account safety and efficacy of the product ***(5).*** The QTPP is organized according to the key sections of a product label and links drug development activities to specific concepts intended for inclusion in a product label. Development of a QTPP can occur early in a product's development, potentially as soon as soon as the product has been identified as a viable candidate for commercialization. A QTPP guides developers to establish strategies and keep development efforts focused and efficient. It is a dynamic summary that changes as knowledge of the drug increases and is used to support the specific statements in labeling. Therefore, a QTPP should be updated at key stages of product development to reflect new information about the drug and changes in the clinical development program. Key inputs of an initial QTPP are, but not limited, to:

- Scientific literature
- Laboratory data
- Preclinical data
- Clinical plan/target population
- Safety profile and product interactions
- Regulatory plan/opportunities
- Regulatory guidelines
- Route of administration/dose delivery
- Device delivery
- Stability data
- Container closure

Once the QTPP is established, the next step is the development of CQAs. They are defined in ICH Q8 as "a physical, chemical, biological, or microbiological property or characteristics that should be within an appropriate limit/range to ensure the desired product quality." Complex cell therapy products have many quality attributes that can potentially impact safety and efficacy. Assessing criticality of quality attributes is best accomplished by using risk-based analysis. I will present an example which uses risk to patient and level of uncertainty to determine the criticality of a product's quality attributes.

The risks associated with a product are tied to the amount of incoming variability caused by materials and process conditions. Therefore, all sources of variability inherent in a formulation or process should eventually be identified and understood. It is therefore important to establish which process parameters and material attributes are "critical." In other words, whose variability has an impact on a CQA and there-

Figure 1 Ishikawa Diagram for CQA – Sterility



fore should be monitored or controlled to ensure the process produces the desired quality. The Ishikawa Diagram is one tool which can be used to identify aspects of the manufacturing process that can impact product quality ***(6).*** I propose how such a diagram can be applied for these cellular therapy products. Taking the results of the Ishikawa Diagram and other inputs, I will also demonstrate how a cause and effect matrix can be used to prioritize criticality of both the process parameters and material attributes which ultimately will be prioritized as critical, presumptive, and noncritical process parameters and material attributes.

Establishing a control strategy is necessary to ensure that the compliance of the product's processing parameters is delivered, and that material attributes are consistently met and remain within their predefined settings. This strategy should include facets that will provide monitoring and/or controlling potential positioned at strategic junctures of a process where criticality can be demonstrated ***(7).*** Using the information gathered from the activities described, I offer an example of a control strategy which includes multiple mechanisms such as:

- Material qualification and testing program (starting materials, raw materials, excipients, etc.)
- Engineering controls (inline filters, environmental conditions, etc.) process qualification
- Procedural controls
- Product testing

The biotechnology industry has realized the benefits of QbD. Developers of cell therapy products can utilize the aspects provided in this article to develop an effective control strategy. From the knowledge gained during development, developers can then revisit and refine this strategy to ensure the predefined product quality objectives are met.

Complex cell therapy products have many quality attributes that can potentially impact safety

References

1. Rathore, A. S. "Roadmap for implementation of quality by design (QbD) for biotechnology products." *Trends in Biotechnology* 27 (2009): 546-553
2. Stanton, J. "Developing an Effective Manufacturing Control Strategy for Cellular Therapy Products." Presentation at the Advanced Therapy Medicinal Products conference, June 3, 2014, 1:30–2 p.m., Madrid, Spain https://europe.pda.org/atmp2014
3. Juran, J.M. *Juran on Quality by Design: The New Steps for Planning Quality into Goods and Services*. New York: Free Press, 1992
4. ICH Tripartite Guideline:Q8 (R1) Pharmaceutical Development, International Conference of Harmonization: 2008
5. Yu, L. X. "Pharmaceutical Quality by Design: Product and Process Development, Understanding and Control." *Pharmaceutical Research* 25 (2007): 781-791
6. Mollah, A.H. *Risk Management Applications in Pharmaceutical and Biopharmaceutical Manufacturing.* Hoboken, N.J.: John Wiley and Sons, 2013
7. Van Buskirk, G., et al. *Best Practices for the Development, Scale-up, and Post-approval Change Control of IR and MR Dosage Forms in the Current Quality-by-Design Paradigm.* AAPS Pharm SciTech, 2014

About the Author

Jean Stanton has been with Johnson & Johnson since 2008 in the Pharma Sector Quality Assurance group responsible for auditing. She was responsible for leading the integration of cell therapy regulations into the processes that supported product development. Her current responsibilities include the maintenance of the Compliance Program for products under development and clinical manufacturing within J&J's Pharmaceutical Sector.

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U.S. FDA Advisory Committee Tackles Tough Questions

Rebecca Stauffer, PDA

The agenda for the U.S. FDA's Cellular, Tissue, and Gene Therapies (CTGT) Advisory Committee meeting in February drew intense interest from numerous outside parties, some of whom spoke at the two-day, public meeting held in Gaithersburg, Md. For the first one-and-a-half days, committee members listened as experts from several universities and research foundations discussed the merits of using mitochondrial manipulation technologies in an effort to allow women with mitochondrial disease—an inherited disorder—to prevent passing on the disease to offspring. This procedure involves combining a healthy donor egg or zygote with genetic material from the mother. Some of the experts suggested the procedure could be used for general fertility treatments as well.

The Advisory Committee was tasked with exploring whether the procedure could move from animal research to human clinical trials. Ultimately, the Committee expressed concerns that while the procedure presents a potential option for reducing transmission of mitochondrial diseases, further study, including additional animal research, is warranted.

Gerald Shadel, PhD, Director, Pathology Research, Yale University, opened the education portion of the meeting by explaining the nature of mitochondrial genetics. This disease affects the mitochondria organelles within a person's cells. Mitochondria play a vital role in energy conversion, including metabolism and respiration. Mitochondrial disease is maternally inherited, hence the research into altering the oocytes in women with mitochondrial disease.

Later that morning, **Shoukhrat Mitalipov,** PhD, Senior Scientist, Division of Reproductive and Developmental Sciences, Oregon Health and Science University, showcased the results of his team's study of mitochondrial gene replacement using primate eggs. The team continues to monitor the health of the four primates born from this study.

Overseas, the United Kingdom is currently working on new regulations that would permit human clinical trials of pronuclear transfer strictly for reducing transmission of mitochondrial disease, according to **Mary Herbert,** PhD, Professor, Reproductive Biology, Newcastle University. This proposal would eventually reach Parliament for a vote.

"If it's passed, detailed regulations would be agreed and adopted by the Human Fertilization and Embryological Authority that would allow them to issue a license…before they would grant a license, they would review the evidence that's submitted to them," she emphasized.

During the public comment portion of the meeting, presenters expressed concern about moving such trials from animals to humans, most voicing concern that while the procedure itself does not constitute genetic engineering, mitochondrial manipulation could serve as the "slippery slope" toward extensive modification of human genes in order for offspring to possess certain traits.

"If one kind of germline change is permitted, it does become more difficult to prevent modification of the nuclear genome," said **Marcy Darnovsky,** PhD, Executive Director, Center for Genetics and Society.

Following the public comment period, Committee members spent considerable time discussing the concerns that a potential mitochondrial manipulation clinical trial would need to address. The Committee felt that while the research for mitochondrial manipulation was compelling, additional animal research is necessary. For a clinical trial to move forward, researchers would have to propose methods to control the manufacturing process and evaluate the final manipulated cells.

Evan Snyder, MD, PhD, Program Director and Professor Stem Cells and Regenerative Medicine Sanford/Burnham Medical Research Institute, and Chair of the Committee, stated in closing that portion of the meeting, that "there was probably not enough data in animals... to move on to human trials without answering a few additional questions."

Early Phase Trials of Advanced Therapies Draw Debate

For the latter half of the second day, the Committee discussed the *Draft Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products.* This draft guidance, issued in July 2013, is intended to assist in the development of early phase clinical trials of gene and cell therapy products that are regulated by CBER. Due to the unique characteristics of these products, early phase clinical trials for these products often differ from those for traditional pharmaceutical products.

The point of this meeting, said **John Hyde,** MD, Office of Cellular, Tissue and Gene Therapies, CBER, was to "at least raise the issues to the point where sponsors think to address them when they have a submission."

The Committee drew consensus on a number of topics addressed in the guidance. First, for Phase I trials, use the set of patients that provides the greatest interpretability. While pediatric patients comprise a vulnerable population, they still should be considered for clinical trials, albeit with extra attention to dose finding studies and informed consent of the patients and their guardians. Panelists also agreed that the sections of the guidance concerning control groups are acceptable, and there is no need for specific guidelines for following up and monitoring; this needs to be done either on a case-by-case basis or determined by the type of cell or gene therapy used.

In addition, during the section of the meeting addressing additional comments, the Committee agreed that the ➤

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Gail Dapolito (Designated Federal Officer)
Center for Biologics Evaluation and Research
Food and Drug Administration

Tabassum Ahsan, PhD Assistant Professor
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Center for Stem Cell Research and Regenerative Medicine

Scott Bruder, MD, PhD (industry representative)
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Foundation Fighting Blindness

Mei-Ling Ting Lee, PhD, Professor
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Early phase clinical trials for these products often differ from those for traditional pharmaceutical products

definition of the appropriate dose for cell products is clear in the guidance document. Committee members also agreed that geriatric patients should be included in future trials. Geriatric populations share similarities with pediatric populations due to informed consent issues. There are also concerns about co-morbidities within this population. Another Committee member then suggested that ways to accelerate trial design should be encouraged. This led to debate about allowing sponsors to share data so that there is less "reinventing the wheel" to avoid repeating steps known to be wrong by other sponsors. As far as how investigators can transition from Phase I to Phase II trials, a Committee member recommended putting together a paragraph or a couple of paragraphs at the end of the guidance addressing the steps that need to be taken before moving to Phase II.

All in all, the two-day meeting of the CTGT Advisory Committee included moments of scientific debate, public concern and consensus. Yet the lively discussions illustrated that the future of drug development lies in these products. Industry and regulatory agencies will need to continue working together to hammer out specific processes to develop advanced therapies in a safe and efficacious manner.

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- Attend Chapter Committee/Planning Meetings
- Technical Report Peer Reviewer

- Speaker
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- Interest Group Leader

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- Membership Committee
- PDA Letter Committee
- Education Committee
- Audit Committee

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

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Protecting the Global Pharmaceutical Supply Chain

Susan Schniepp, Allergy Laboratories, and Program Committee Member

2014 PDA/FDA Pharmaceutical Supply Chain Conference • Washington, D.C. • June 3–6 • www.pda.org/supplychain2014

Is your company aware of the multitude of challenges in protecting and securing the integrity of your product in the global marketplace? Is it aware of the latest science- and risk-based approaches in proactively addressing new laws, regulations and guidances governing distribution and importation practices?

Learn to develop a robust supplier management process as well as strong good distribution and storage practices with two PDA TRI courses on June 5–6. For more information on these courses and to register, please visit www.pda.org/supplychaincourses2014.

Global regulators, health authorities and trade organizations are working collaboratively to actively solve complex supply chain issues, including management of temperature-sensitive product, cargo theft, supplier selection and ongoing monitoring.

To address these issues, PDA, the U.S. FDA and Rx-360 have teamed up to develop an exciting, educational and informative program for the *2014 PDA/FDA Pharmaceutical Supply Chain Conference*. The 2014 conference builds on previous conferences and educates attendees on the next strides the industry and regulators are taking to secure the global supply chain.

The Program Planning Committee has confirmed expert speakers representing a unique cross section of the pharmaceutical industry in addition to supply chain experts in related businesses. These renowned individuals will be presenting during scheduled plenary sessions. Each plenary session is formatted to offer participants maximum opportunity for questions and answers through panel discussion imbedded as a part of most of the plenary session.

There are nine plenary sessions in all, starting with the opening plenary session exploring the issue of counterfeit drugs via a real example from a major company on how one of their products was counterfeited. The conference is designed to present the most current information that will be discussed in more detail at the end of the plenary session. Instead of multiple breakout groups, there are only two topics where participants will choose which topic they wish to hear more details about: Cold Chain Management and Cargo Theft. This unique approach assures that all participants hear the same concerns and cures for managing the complicated global supply chain in today's environment.

Regulatory Briefs

Regulatory briefs are compiled directly from official government/pharmacopoeial releases. Links to additional information and documentation are available at www.pda.org/regulatorynews.

Key Regulatory Dates

Comments Due

June 12 — Guidance Addresses Injectable Vial Packaging

North America

U.S. FDA and EMA Extend QbD Pilot Program

The U.S. FDA and EMA have agreed on a two-year extension of the joint pilot program between the two agencies concerning parallel evaluation of QbD applications effective April 1. This joint pilot began in March 2011 as an effort to share knowledge, ensure harmonization with international QbD guidelines and promote availability of drug products with consistent quality in both the United States and the European Union. While the program has led to agreement between the two agencies on a number of QbD topics, there remain areas still in need of harmonization, thus the decision to extend the pilot program.

Guidance Addresses Injectable Vial Packaging

In mid-March the U.S. FDA released the draft guidance *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products*. This guidance serves to clarify the Agency's requirements for allowable excess volume in injectable vials, in addition to emphasizing the importance of appropriate package sizes for drug and biologic products. The document specifically targets fill and packaging issues for injectable products packaged in vials and ampules. Comments due June 12.

Europe

EMA Publishes Process Validation Revision

In late February, the EMA published its revised process validation guideline. This revision emphasizes continuous process verification and incorporates modern GMP aspects into the guideline, including integration of ICH Q8–Q10, process analytical technology (PAT), QbD, real-time release testing, inclusion of the Annexes and harmonization with the U.S. FDA's process validation guidance. This revised guideline will then come into effect in August.

International Inspections

PIC/S Cofounder Passes Away

Hans Smallenbroek, one of the founders of PIC/S, passed away on March 19. He was 62 years old. He served as PIC/S Chairman from 2004–2005 and as a Member of the PIC/S Executive Bureau from 2000–2009. In addition, he served as the Co-rapporteur for assessing the membership application of the U.S. FDA.

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- Pharmaceutical Statistics: Process Optimization by Design (July 17-18)

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AUGUST 2014

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www.pda.org/dryheat

This hands-on course focuses on the microbiology and engineering qualification of dry heat depyrogenation processes. You will be given a foundational understanding of depyrogenation science that will then be applied in the design and verification of equipment, depyrogenation process development, process performance qualification for new systems and ongoing maintenance of the validated process.

An Introduction to Visual Inspection

August 27-28 | Bethesda, Maryland
www.pda.org/visual

This course covers the fundamentals of visual inspection and their application to injectable products. It will be a combination of lecture/discussion and hands-on laboratory exercises used to develop and practice practical inspection skills. The skills developed through this course may be applied to both manual human inspection and automated machine inspection.

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

Laboratory Courses

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This is your opportunity to own a comprehensive, single-source compilation of PDA sterilization Technical Reports available.

Over the years, PDA expert task forces have developed several technical reports on moist and dry heat sterilization processes.

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This volume is a convenient and powerful reference for individuals working with sterilization processes for pharmaceutical products. This compilation will be an invaluable guide for you to navigate the scientific and regulatory aspects of traditional and alternative sterilization methods.

This hardbound series bundles the five PDA technical reports as well as selected articles from the *PDA Journal of Pharmaceutical Science Technology*:

- ☑ **Technical Report No. 1:** Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control
- ☑ **Technical Report No. 3 (Revised 2013):** Validation of Dry Heat Processes Used for Depyrogenation and Sterilization
- ☑ **Technical Report No. 30 (Revised 2012):** Parametric Release of Pharmaceutical and Medical Device Products Terminally Sterilized by Moist Heat
- ☑ **Technical Report No. 48:** Moist Heat Sterilizer Systems: Design, Commissioning, Operation, Qualification and Maintenance
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PDA Comments on Health Canada Guidance

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

April 9, 2014

Bureau of Pharmaceutical Sciences Therapeutic Products Directorate Health Canada Address Locator 0201D 101 Tunney's Pasture Driveway Ottawa, Ontario K1A 0K9

Reference: Health Canada Quality (Chemistry and Manufacturing) Draft Guidance Document: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)

Dear Sir/Madam,

PDA appreciates the opportunity to comment on this draft guidance which is intended to update and consolidate existing guidance documents as well as to clarify information provided in Module 3 of the CTD. 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 comments were prepared by a committee of experts on behalf of our Regulatory Affairs and Quality Advisory Board and Board of Directors.

PDA recommends that discussion of GMP requirements should be left out of this guidance and included in HC Good Manufacturing Practices Guidelines GUI-0001 to avoid misunderstanding between the contents of a submission to support licensure and the requirements for routine manufacture at a site. In some sections of this guidance, especially in the manufacturing and controls section P.3, the level of detail seems to require inclusion of GMP information in the submission dossier. Specific examples are noted in the attached comments.

PDA additionally suggests using ICH standard terminology throughout the document. For example, use the Q7 term Active Pharmaceutical Ingredient (API) consistently instead of active ingredient, active substance or active moiety. PDA believes following internationally accepted standards is clearer to applicants and avoids misunderstandings or misinterpretation. In those instances where adoption of international terminology is not feasible, we recommend that the rationale for using alternate terminology be provided to ensure that any difference in meaning can be fully understood by the reader.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard M. Johnson President, PDA

PDA Commenting Task Force

Jeffrey Broadfoot, Cangene
Christopher Leonienco, Cangene
Barbara Jentges, PhD, PhACT GmbH
Susan Schniepp, Allergy Laboratories
Antonella Maggio, J&J Canada

Junko Sasaki, Dainippon Sumitomo Pharma

Building Global Connections Through Chapter Involvement

I am honored to have a precious chance to contribute to the *PDA Letter* at this time.

I am a Director, both on the PDA Board and the Japan Chapter, which represents over 700 pharmaceutical professionals in Japan. I act as a bridge between the two. So, I would like to write about PDA's "people activity" for the Voices of the Board.

First, chapter activity and collaboration is undoubtedly growing. Last year, the PDA Chair said at the *PDA/FDA Joint Regulatory Conference* that "throughout globalization, consideration to change is needed for industry, authorities, persons and technology." From the view of the PDA Japan Chapter, I believe that it is very important to understand each other's background and differences in order to arrive at better and effective solutions, and also to consider global views for sustainable improvement.

Under these circumstances, PDA is continuing to support chapter activities by establishing new chapters, holding chapter meetings in conjunction with signature conferences, like the PDA/FDA Joint Regulatory Conference, and participating in chapter events. I believe the mutual activities and collaboration between the Association and chapters to be a great benefit for all of us.

I want to talk about my own experiences. I have deeply understood the importance of more global thinking and have been participating in PDA conferences in the United States, Europe and Japan. I've also had opportunities to expand my understanding due to involvement in chapter activities. When I participated in the PDA Annual Meeting, I was impressed by the productive activities and was welcomed with great hospitality. PDA's collaborative efforts provide attendees presentations from regulatory authorities. At a meeting in Italy that I recently attended, I was excited to talk with members of the Italian Chapter. It was valuable to discuss the activities and/or needs of our chapters at that time.

When we want to deepen mutual collaboration, it is always very important to understand each individual activity within the chapter. As an example, I am pleased to share the Japan Chapter activities at this time. The chapter includes the Technical Education Committee, Kansai Study Group, ERES (electronic record/or signature) Committee, QAQC Committee, API GMP Committee, Biovirus Committee, Aseptic Products GMP Committee, Medical Devices Committee, and the Development QA Committee. Members of each committee hold a face-to-face discussion every month or two. And the outcomes of these meetings are provided in subsequent conferences or the Chapter's annual meeting with close collaboration with Japan authorities.

By gaining visibility for these chapter activities, this can lead to inspiration for more effective approaches. Communication is a useful tool regardless of time difference or distance.

The *PDA Letter* is also a good way to understand each chapter's activity. If you want to communicate or build a relationship with PDA and its chapters, please email **Trevor Swan,** PDA's Manager of Membership and Chapters at swan@pda.org. PDA and its Japan Chapter would appreciate hearing your needs, input and suggestions for creating more effective chapter and global PDA collaboration.

Lastly, we, PDA, will strengthen our contribution to PDA members with our connecting force as members of PDA and each chapter activities. This will bring us more harmonized global knowledge.

Your Local PDA Connection

Are you curious about the issues unique to your region?

Another layer of PDA leadership resides at the grassroots level in the Chapter organizations. Regional PDA Chapters provide local services to the membership, including translations of PDA publications, networking social events, student scholarship and annual regulatory and technical conferences. Each Chapter is managed by volunteer leaders.

Learn more about your local Chapter at www.pda.org/Chapters

Cadre of Members Advancing Advanced Therapies

The Smithsonian Institute's American History Museum just closed an exhibit celebrating the birth of biotech, sponsored by Genentech. The small exhibit included equipment used to produce recombinant insulin, one of the first major biotech products to hit the market over 30 years ago. Now, biotech products make up a significant part of the pharmaceutical industry, and those manufacturing them represent a large part of the PDA membership, since most biotech drugs are injectables.

Anyone wondering what it was like being in the industry at the dawn of the biotech revolution need only look at the growing number of advanced therapeutics under development. While only a few cellular, gene and other advanced therapies have actually gotten onto the market, there is strong momentum in this product type. For several years, PDA Europe has sponsored a scientific conference on ATMPs. I was pleased to cover the 2013 event, and due to the fascinating nature of the subject matter, advocated making the theme for this issue ATMPs to help promote the 2014 event in Madrid.

Right now, only a small cadre of the membership is involved with ATMPs, but when you consider the promise of these product types, my guess is that this group will grow much larger in the years to come, just like the number of biotech professionals in PDA has grown.

This issue covers a lot of ground regarding ATMPs, with articles on regulatory standards, manufacturing controls, the activities of the ATMP Task Force, information on the upcoming PDA Europe event in Madrid, a report from FDA's most recent advanced therapies advisory meeting, and an InfoGraphic on the state of advanced therapies.

ATMP developers must be aware of supply chain issues, even if most of their supplies come from the patients themselves. But the industry as a whole needs to continue to vigilantly monitor the supply chain to protect patients. PDA has teamed up with the U.S. FDA in recent years to help with those efforts. Several articles in this issue highlight the relevant topics and the upcoming supply chain meeting.

It was a pleasure to once again attend the *PDA Annual Meeting*. It was my 11th since joining PDA in 2003. Each year, I enjoy the interaction with the members and the feedback received. For the second time, I held a "publishing with PDA" luncheon, and I was pleased to meet members of the *PDA Letter* Editorial Committee whom I hadn't met before. The luncheon produced many great ideas to guide Journal Editor **Govind Rao** and the *PDA Letter* editors in our publishing activities. This kind of face-to-face feedback in the age of webinars, tweets, and other electronic communication remains invaluable. I thank **Maik Jornitz, Leticia Quinones, Ross Acucena,** and **Michael DeFelippis** from the PLEC for making time for the session. Look for more coverage of the Annual Meeting, including an extended "PDA Photostream" in upcoming issues.

PDA Letter

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

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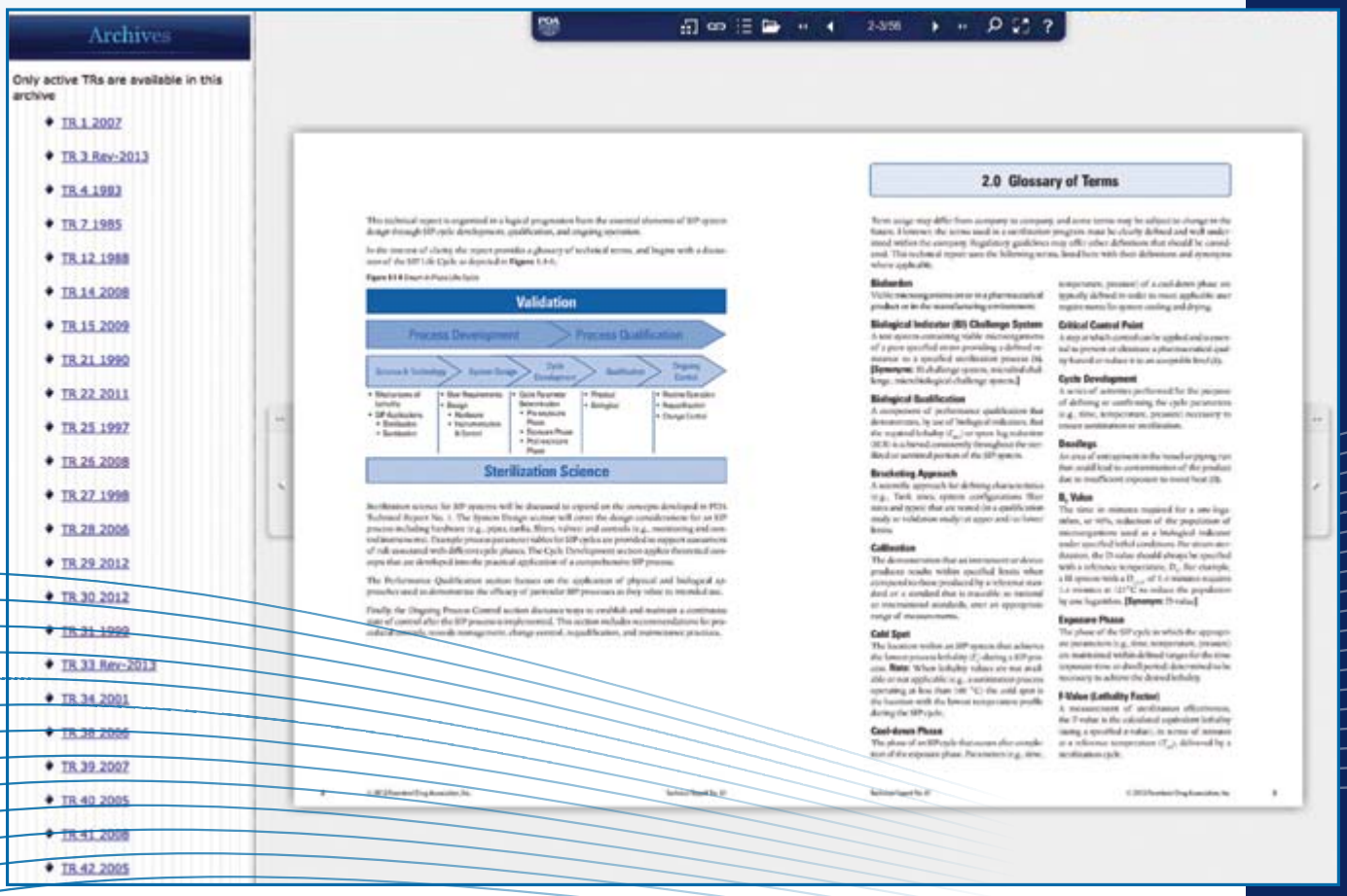

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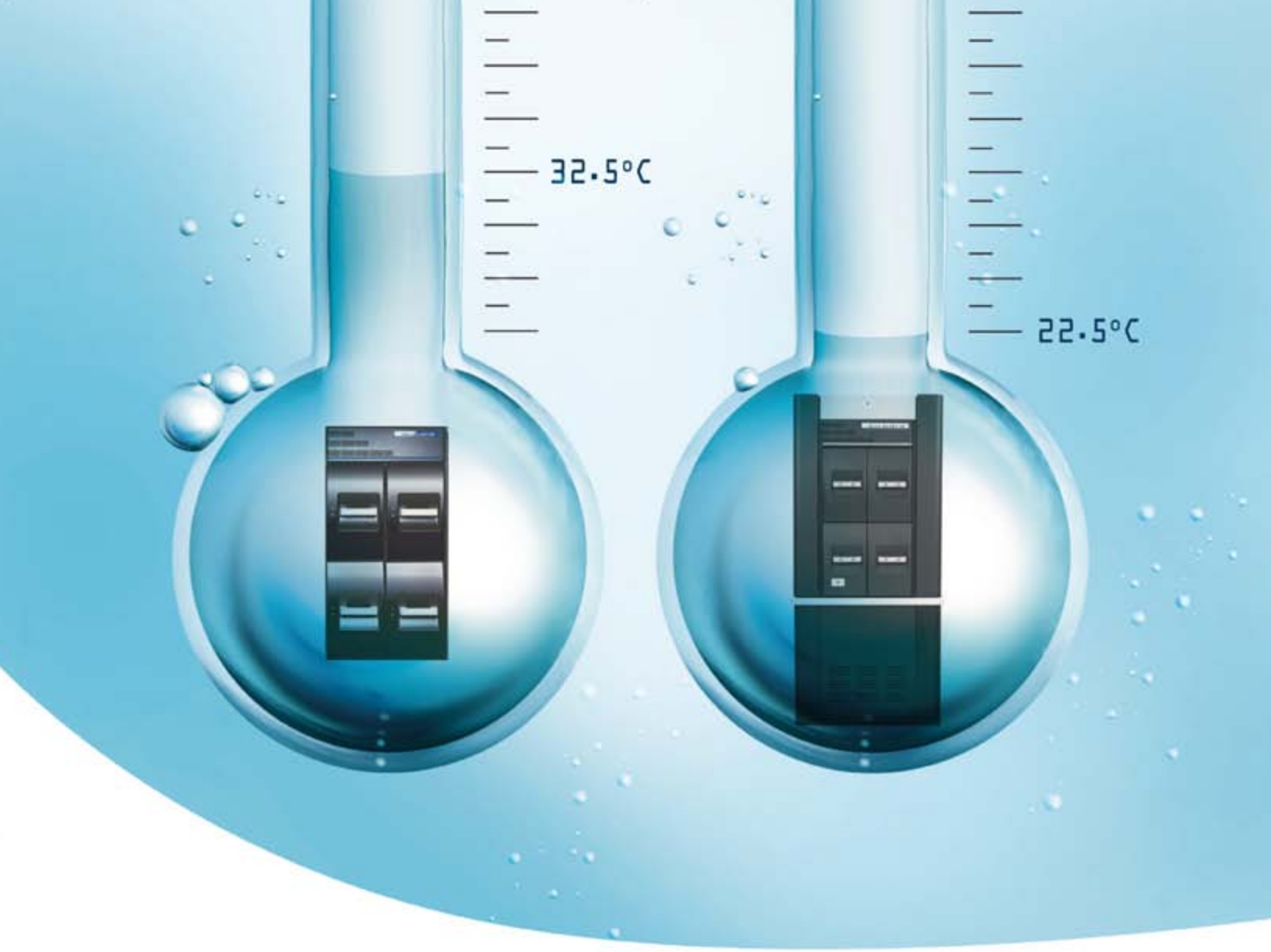

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