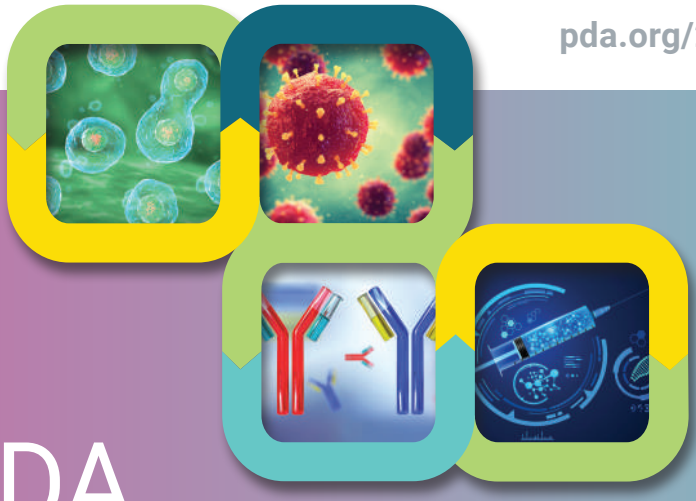
People • Science • Regulation

PDA Letter

Volume LV • Issue 4 www.pda.org/pdaletter April 2019

THE PHARMACOPEIA IN THE 21ST CENTURY 22

pda.org/2019BiopharmWeek



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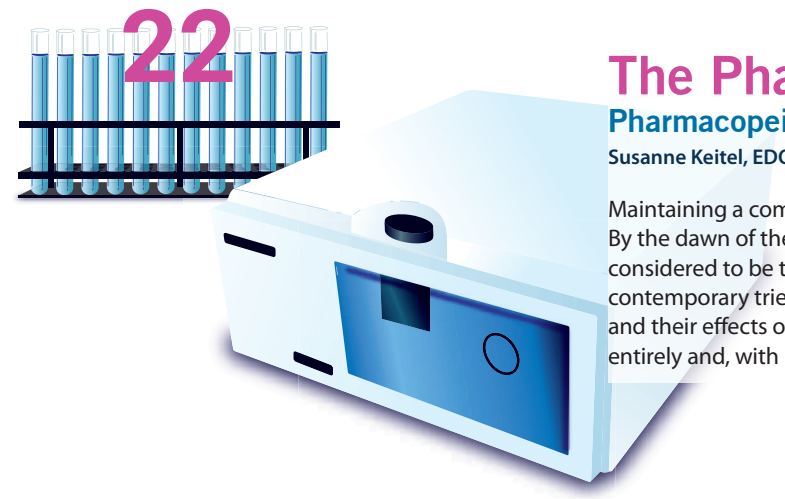
April 2019 PDA Letter



The Pharmacopeia in the 21st Century

Pharmacopeias Move to Modernize in Changing Times

Susanne Keitel, EDQM

Maintaining a comfortable state of health has always been a major human preoccupation. By the dawn of the first millennium, this was manifested in *De Materia Medica,* generally considered to be the earliest example of a pharmacopoeia. This treatise compiled contemporary tried and tested herbal and other remedies, methods for their preparation and their effects on patients. Fast forward two thousand years and the world has changed entirely and, with it, attitudes about health and well-being.

Cover Art Illustrated by Katja Yount

Future Lies in Continuous Manufacturing Technology

What do the Global Regulators and Pharmacopeias Have to Say?

Bei Ma, Pinea Group

In recent years, the pharmaceutical manufacturing leaders have been exploring innovative and new technical solutions to achieve better quality, improve productivity and operational efficiency, increase process throughput and yields.

Advancements in technologies such as, digitalization, artificial intelligence and machine learning, 3D printing, precision medicine, automation, augmented and virtual reality, will shape the pharmaceutical industry over the next five to ten years.

Growth Promotion Testing For EM

Reference Materials Critical for Ensuring Effective Environmental Monitoring Tests

Brendan Tindall, biomerieux, and Graham Vesey, Regeneus

Growth promotion testing of culture media is an important part of microbiological testing in support of pharmaceutical quality. The growth promotion test is a quality control requirement that confirms the ability of a new batch of media to support growth of a predetermined selection of representative microorganisms.

InfoGraphic

Avoid These 5 SOP Pitfalls

Learn what mistakes to avoid in order to ensure an effective SOP for your GMP operations.

PDA Letter

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Digital Exclusives

> Industry and Regulators Convene to Address Vaccines Challenges
Read a summary of last year's *Vaccines* conference in this longform article!

pda.org/letter

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A Whole Globe of Pharmacopeias

Rebecca Stauffer @RebeccaStauPDA

Last May, I was grateful to attend the inaugural PDA Europe *Pharmacopoeia Conference* in Vienna. The planning committee, including co-chairs **Susanne Keitel** and **Janeen Skutnik-Wilkinson,** and staff put together a strong program featuring representatives from pharmacopeias in North America, Europe, Asia and Africa. So much was covered in the sessions that I found it challenging to draft a small summary. I, in fact, had to publish the article in two parts to effectively capture the amount of information covered in the two-day event ***(1,2).***

In light of the second PDA EU *Pharmacopoeia Conference* in May, I recently reviewed those articles in preparation. I would like to share some highlights.

First, Keitel (who also provided this issue's cover story on p. 22) provided an overview of the European Pharmacopoeia (Ph. Eur.), its origins, and how it operates in relation to the Council of Europe. The Ph. Eur. does not actually fall under the European Union, which means that the United Kingdom will continue to include the Ph. Eur. in the British Pharmacopoeia regardless of Brexit. Similar updates were provided by representatives of the other pharmacopeias on hand.

Attendees had the unique experience of learning about the formation of a new pharmacopeia for the country of the Eurasian Economic Union (EAEU). **Ardak Tulegenova,** Deputy Chairwoman of the EAEU Pharmacopoeia Committee, explained how the member countries (Armenia, Belarus, Kazakhstan, Kyrgyzstan and the Russian Federation) are working to develop a pharmacopeia specific to that region. This regional pharmaceutical market seeks to harmonize with ICH, EMA, WHO, the U.S. FDA and other bodies.

While learning about the various pharmacopeias worldwide, representatives from companies, including Merck and Novartis, reminded everyone of the challenges involved with meeting standards from global pharmacopeias and how they manage to do it.

Overall, it was an excellent inaugural meeting where discussion carried over into refreshment and meal breaks. Passionate points were raised during the Q&A, and I could tell attendees could have kept the meeting going on for weeks, if allowed!

I can only imagine all the great topics and information that will be presented at this year's *Pharmacopoeia Conference* in May. The meeting will be held in Geneva, which should have pleasant weather, although as those of us who attended the networking event at the 2018 *Pharmacopoeia Conference* can attest, there is always the possibility of a sudden thunderstorm, particularly when seated outdoors at a restaurant!

References

1. Stauffer, R. "Industry Converges on Pharmacopeial Convergence." *PDA Letter* (Aug. 21, 2018) https://www.pda.org/pda-letter-portal/archives/full-article/industry-converges-on-pharmacopeial-convergence
2. Stauffer, R. "A Deep Dive into Pharmacopeial Harmonization." *PDA Letter* (Sept. 11, 2018) https://www.pda.org/pda-letter-portal/archives/full-article/a-deep-dive-into-pharmacopeial-harmonization

Jack Cole, In Memoriam

PDA is saddened to announce that former PDA President **Jack Cole** passed away March 16. He served as PDA President from 1979-1981 and was a long-time volunteer during a period of expansion for the Association. For many years after serving in his leadership role, Jack remained a passionate cheerleader for PDA, even recruiting his son to help design the Association's logo that remains in use today.

Jack was instrumental, along with other PDA leaders, in establishing the PDA Foundation for Pharmaceutical Sciences to advance education programs in parenteral sciences. In addition, he sought to expand PDA's course offerings overseas by chairing an ad hoc committee tasked with developing a cooperative technical exchange program. Jack was particularly interested it bringing PDA services to Latin American, and he conducted a series of lectures at the pharmacy schools of the Universities of Buenos Aires and Sao Paulo.

In 1996, PDA awarded him Honorary Membership in recognition of his extensive work for PDA.

Jack became an active member and volunteer with PDA in the late 1960s while working for Millipore. He then spent the rest of his career with Pall Corporation while continuing to volunteer for PDA.

He is survived by his wife Vered, and sons Keren and Elan.

Jack's commitment to PDA can be reflected in the drawer of valuables that included all of his ten-, 20-, 25-, 30-, 35- and 40-year PDA lapel pins and tie clips. He always kept the PDA family close in heart and mind.

A memorial service was held at Gutterman's in Woodbury, N.Y., on March 18. Donations in his name can be made to the Visiting Nurse Service of Suffolk County New York (505 Main Street, Northport, NY 11768) and Memorial Sloan Kettering New York (https://giving.mskcc.org/ways-to-give).

The 2018 *PDA Letter* Article of the Year

PDA and the *PDA Letter* editors congratulate **Pieter-Jan Van Bockstal,** Ghent University, **Jos Corver,** RheaVita, and **Thomas De Beer,** Ghent University, authors of "New Approach Suggests Continuous Lyophilization is Possible." This article has been recognized as the *PDA Letter* Article of the Year for 2018.

The article served as the cover story for the March 2018 issue and summarizes an innovative continuous process for freeze-drying biologic drug products.

Each year, the *PDA Letter* editors and the Editorial Committee identify the top articles published that year based on reader interest and select the one that best encapsulates PDA's mission of connecting People, Science and Regulation®.

PDA Volunteer Spotlight

Andiyanto Sutandar, PhD

- **Technical Director**
- ***HGP Asia***
- Member Since | **2014**
- Current City | **Singapore**
- Originally From | **Pontianak, Indonesia**

I enjoy helping the industry grow in the area of risk management

What are your current volunteer activities with PDA?
I have volunteered with PDA since 2015 when I began helping organize events for the Singapore Chapter. Now, I am the Treasurer of the Singapore Chapter. I also volunteer on the *PDA Letter* Editorial Committee.

What has been your most memorable experience volunteering for the chapter?
Organizing the Singapore Chapter's data integrity and computer systems validation symposium has been very memorable to me. Although the chapter knew the topic would be interesting to many stakeholders in Singapore, we never imagined that we would have close to 60 attendees—requiring us to rework the seating and venue arrangement!

How did you learn about PDA?
I first encountered PDA when I read *PDA Technical Report No. 49: Points to Consider for Biotechnology Cleaning Validation.* TR-49 supports a lot of my work, and I soon discovered that PDA has many more industry-relevant technical reports, so I decided to join.

How have PDA publications helped you?
I have used PDA documents extensively in my professional career. As the industry is grows into a risk- and science-based approach, PDA documents like the aforementioned technical reports and the *PDA Journal of Pharmaceutical Science and Technology* remain highly relevant.

What inspired you to choose your current career path?
I enjoy working in the field of risk management. In the pharmaceutical industry, risk management directly impacts human lives. In my current role as Technical Director, I can impart a risk management perspective to my colleagues. In addition, my role allows me to be involved in the various technical aspects of the projects and initiatives in my organization.

What do you like to do in your free time?
I like to cook simple food that can be enjoyed by my family and friends.

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Chapter Update

Published online first

NE Election Results Revealed at Cold Storage Event

Henry Brush, Zagfen, New England Chapter Member-at-Large

As the weather turned from crisp to cool in mid-November, PDA's New England Chapter learned about deep cold storage conditions and welcomed the chapter's new Board of Directors.

On Nov. 14, the chapter held a dinner meeting on the topic, "Parenteral Packaging for Deep Cold Storage," in Marlborough, Mass. Before the evening's two presentations, outgoing President **Amnon Eylath** thanked both outgoing and new members of the chapter's Board of Directors for their dedication to the chapter.

The previous board consisted of:

- **Laurie Masiello**, President-Elect
- **Kathleen Souza,** Secretary
- **Shawn Sherry,** Treasurer
- **Elisabeth Piquet,** Member-at-Large
- **John Masiello,** Member-at-Large
- **Roger Deschenes,** Member-at-Large
- **Steven Jones,** Member-at-Large

John Masiello, who headed the Chapter Nomination Committee, introduced the new Board of Directors: incoming President Laurie Masiello, President-Elect Steven Jones, returning Secretary Kathleen Souza, Treasurer **Tayaba Naz** and Members at Large **Mary Griffin**, **Brian Clark** and **Henry Brush.** He explained that the Board is elected to a two-year term, and the President-Elect will serve as the next President in two years.

Following the announcement of the election results, **Roger Asselta** gave a fascinating presentation on "Impact of Deep Cold Storage Conditions on the Container Closure Integrity of Parenteral Vials." He opened with a tutorial on the fundamentals of stopper material properties, mechanics of vial sealing, container closure integrity testing methods and regulatory expectations for container closure. Appropriate parenteral vial sealing occurs at several surfaces between the stopper and vial. The transition seal is the primary sealing surface and relies on deformation of the elastomeric stopper material to achieve an appropriate seal. Asselta explained that residual seal force is the stress that the elastomeric material of the vial stopper continues to exert on the land seal surface of the vial after the aluminum cap has been crimped onto the vial. Vial storage temperature near or below the glass transition temperature of the elastomeric stopper material can have a negative effect on the sealing properties due to the change in viscoelastic properties of the stopper. Other factors that impact sealing properties are the effectiveness of the crimping process, dimensional fit of the stopper and vial combination and dimensional variation of the components.

With additional advances in therapies that require cryogenic storage temperatures, ➤

more work is required to identify appropriate packaging materials that can reliably withstand deep cold storage. Ongoing work includes understanding why some traditional vials maintain their container closure integrity, developing new materials with lower glass transition temperatures and even rethinking the entire approach to how drug products are packaged for storage at cryogenic temperatures.

Following Asselta, **Joe Cintavey** presented "Minimizing Risk of Product Loss in Cold-Chain Handling," which covered challenges related to drug substance transport at cryogenic temperatures.

Many of the containers used for drug substance transport are single-use, polymer-based packaging solutions that face have similar challenges as vial-based containers. At cryogenic temperatures, the polymer-based materials approach or exceed the glass transition temperature, causing them to become brittle and potentially lose their integrity due to cracking of the material. Two major concerns are the extractable and leachable materials associated with the materials and interactions between the drug and the packaging material. One potential solution is a fluoropolymer-based material that has high purity and relatively low glass transition temperature. Cintavey presented fit-for-use criteria used during product development to identify a material and design that will address product application challenges. Test data presented included a drop test to demonstrate durability, temperature mapping to confirm uniform freezing of product within the container and mechanical integrity of the container when exposed to freeze/thaw cycling.

The chapter thanks Henry Brush and **Melissa Lincoln-Kemp** for serving as meeting hosts.

PDA Who's Who

Roger Asselta, Vice President of Technical Affairs, Genesis Packaging Technologies

Henry Brush, Director, Drug Product Manufacturing, Zafgen

Joe Cintavey, Product Manager, GorePharm Bioproducts

Brian Clark, Principal Consultant, GMP Operations Consulting

Roger Deschenes, Senior Specialist, External Quality. External Laboratories, MSD

Amnon Eylath, AVP, Karyopharm Therapeutics

Mary Griffin, Principal, M.G. Quality Microbiology Consulting

Steven Jones, Manager, Validation Support

Melissa Lincoln-Kemp, Account Executive, Catalent Pharma Solutions

John Masiello, EVP, Masy BioServices

Laurie Masiello, President and CEO, Masy BioServices

Tayaba Naz, MilliporeSigma

Elisabeth Piquet, Consultant

Shawn Sherry, Business Development Manager, Overlook Industries, Inc.

Kathleen Souza, R&D Manager, Virology & Microbiological Sciences, MilliporeSigma

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To learn more and register, please visit pda.org/2019RapidMicro

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EXHIBITION: OCT. 23-24
TRAINING COURSES: OCT. 25
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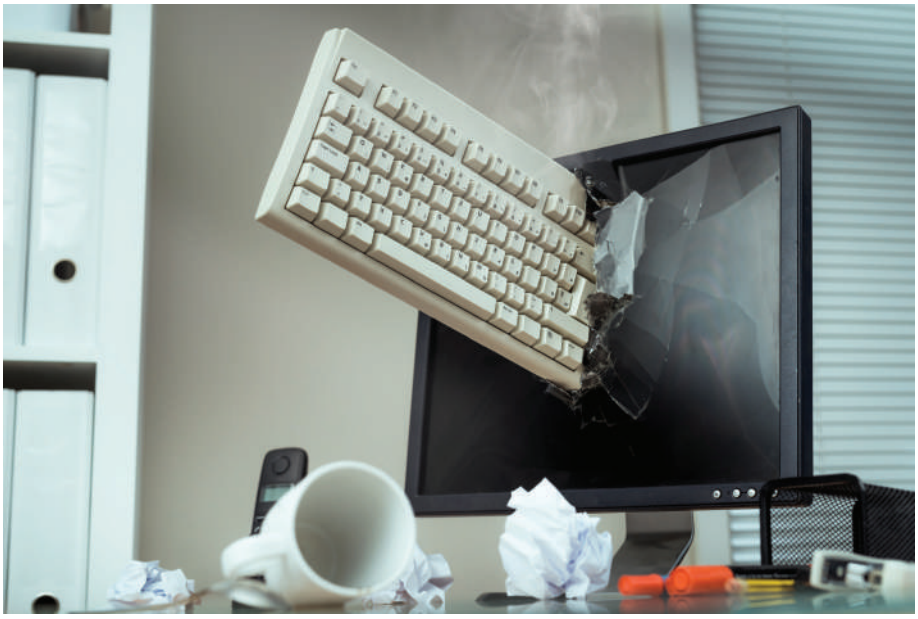
4 Simple Strategies for Overcoming Stress

Jeremy Kingsley, OneLife Leadership

The inbox on your desk—and the one in your email—are both full of things that need to be dealt with. Your calendar shows that you are booked solid for the next week and a half. You have employees to meet with, potential new ones to interview and a million other things to do, but little time to do them in. It is no wonder that you are stressed out. Thankfully, there are a few things that can help you manage your stress levels. Take the time to follow these tips, before you end up taking your stress out on others.



1 Step Away from the Computer for Ten Minutes Every Few Hours

Studies have shown that spending all of your time chained to your office desk and computer raise your stress levels— even if you are being productive. A short, ten-minute break spent on your feet and away from your desk will help considerably. Socializing is a good stress reliever as well, so consider spending your ten-minute break drinking coffee and talking to your coworkers.

2 Schedule Relaxation Time

Whether you set aside a few hours on the weekend to play golf, watch a movie, or read a book, it is important that you take the time to clear your head. Busy people tend to follow their calendars religiously, so add some "fun time" to yours. Otherwise, you may never have a chance to relax.

3 Exercise in Your Off Time

Instead of lounging in front of the television set when you get home, spend some time in the gym. Exercise is a proven stress reliever, and you would be surprised how cathartic it is to take out some of your stress-induced aggression on a punching bag, in a spin class or on the treadmill.

4 Watch Something Funny

The old saying is that "laughter is the best medicine." This is still very much the case, as it is a proven way to relieve stress and brighten your mood. Whether you watch a short video on YouTube or listen to a friend tell jokes, you will feel some of the stress melt away as you laugh.

As you can see, overcoming stress is not completely impossible. Following at least one of these tips on a regular basis will lower your stress levels, thus turning you into a better boss or employee. You will feel better and be more productive.

About the Author

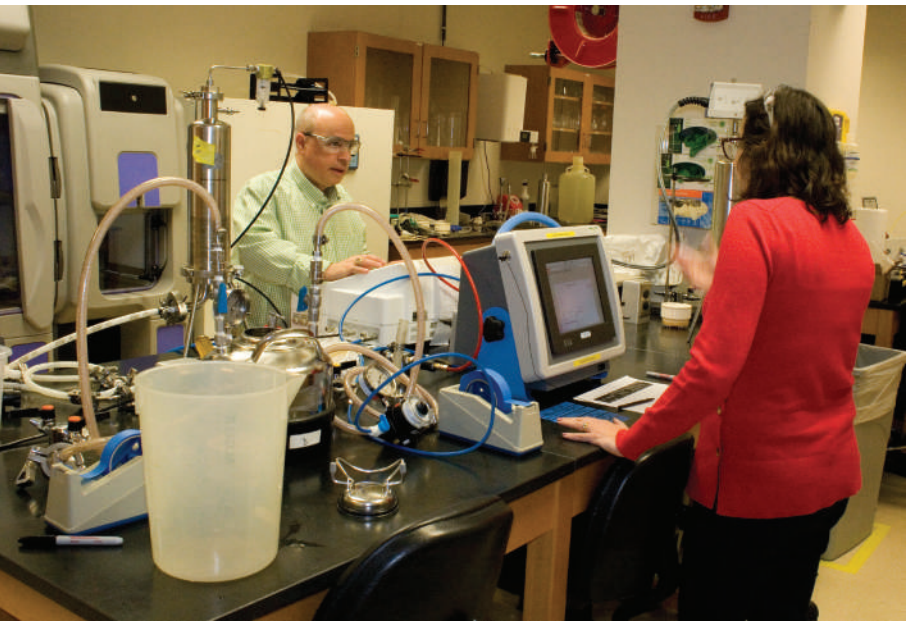
Jeremy Kingsley is a professional speaker, leadership expert and bestselling author. Learn more at www.jeremykingsley.com.

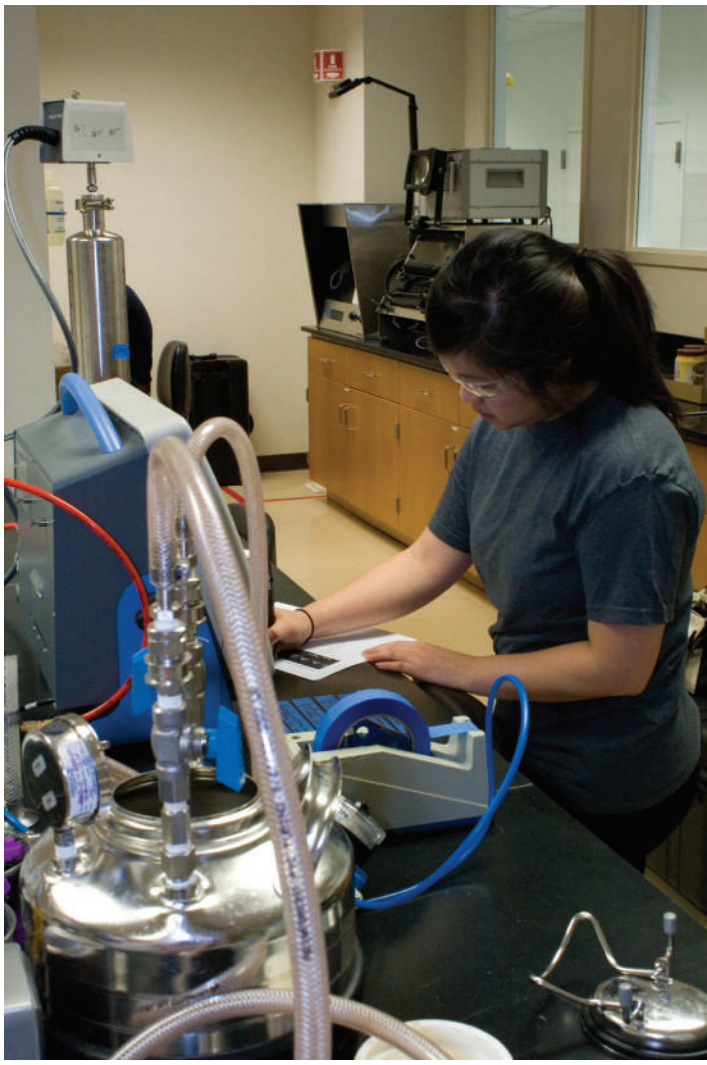
PDA Photostream www.flickr.com/parenteral-drug

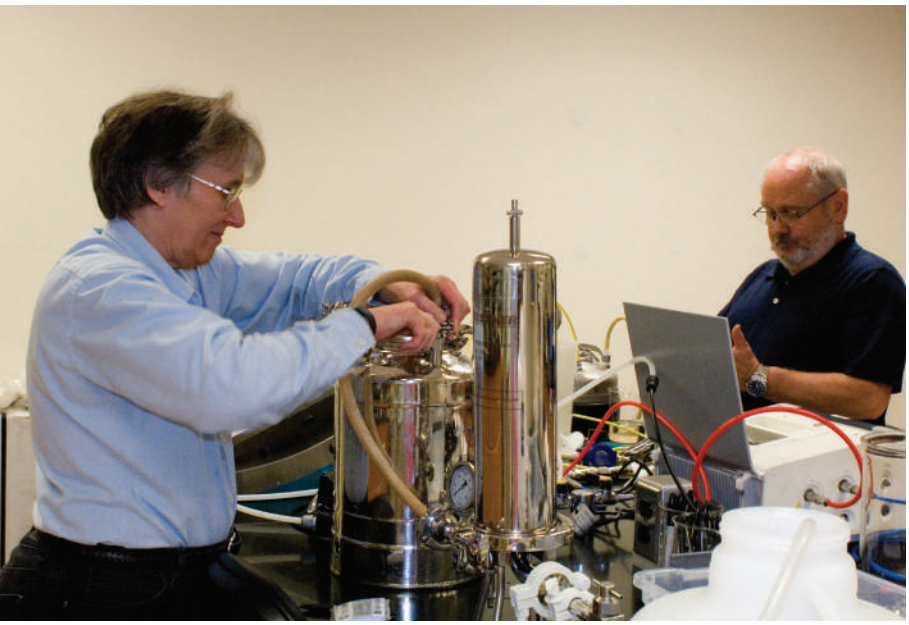
PUPSIT Testing

February 25–27 | Bethesda, Md.

During the last week of February, a team of PDA volunteers conducted a masking study to determine if preuse, post-sterilization integrity testing (PUPSIT) presents a potential contamination risk to product. The study took place on site at PDA HQ. Results will be released at a future date.







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Standard 02-201x, Cryopreservation of Cells for Use in Cell Therapies and Regenerative Medicine Manufacturing Task Force

February 8 | Bethesda, Md.

Members of the task force behind PDA's upcoming standard on cryopreservation of cells met in-person at PDA's headquarters to further develop this new standard, one of the first PDA plans to release. Stay tuned for more information on this exciting project!

SNAPShot

Published online first

PDA Addresses LER in TR, Forthcoming Book

Since 2013, low endotoxin recovery (LER) has been a hot topic within the industry. Failure to detect spiked endotoxin in some finished sterile biologics despite testing with the *Limulus* amebocyte lysate (LAL) assay has proved alarming across industry and with regulators.

PDA is excited to announce the release of *Technical Report No. 82: Low Endotoxin Recovery.* The task force spent innumerable hours working on this document and hopes it helps biologics manufacturers address this potential concern in their processes. Not only does the technical report offer steps to address the problem but it also includes 12 case studies conducted by biologics manufacturers.

By the end of March, *PDA Technical Series: Endotoxin Analysis and Risk Management,* a compilation of papers from the *PDA Journal of Pharmaceutical Science and Technology.*

Both the technical report and the book will be available in the PDA Bookstore (www.pda.org/bookstore). PDA members also have 30 days to download a free copy of the technical report as part of their membership benefits.

Journal *Top 10*

Particulate Papers Dominate PDA Journal Views for February

Below are the top ten articles from the *PDA Journal of Pharmaceutical Science and Technology* (journal.pda.org) for the month of February.

1. PDA Paper

Stan Bukofzer, et al. "Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products" (January/February 2015)

2. Review

Stephen E. Langille, "Particulate Matter in Injectable Drug Products" (May/June 2013)

3. Research

Robert Ovadia, et al. "Quantifying the Vial Capping Process: Residual Seal Force and Container Closure Integrity" (January/February 2019)

4. PDA Paper

Deb Autor, et al. "PDA Points to Consider: Best Practices for Document/Data Management and Control and Preparing for Data Integrity Inspections" (May/June 2018)

5. Research

David R. Machak and Gary L. Smay, "Failure of Glass Tubing Vials during Lyophilization" (January/February 2019)

6. Research

Philippe Lam and Thomas W. Patapoff, "Split-Cakes, Still Delicious" (January/February 2019)

7. Research

Richard O. Montes, et al. "Simple Approach to Calculate Random Effects Model Tolerance Intervals to Set Release and Shelf-Life Specification Limits of Pharmaceutical Products" (January/February 2019)

8. Technology/Application

Diane Paskiet, et al. "Assessment of Extractable Elements from Elastomers" (January/February 2019)

9. Research

Patricia Mattiazzi, et al. "Extraction/Leaching of Metal-Containing Additives from Polyvinyl Chloride, Ethyl Vinyl Acetate, and Polypropylene Bags and Infusion Sets into Infusion Solutions" (January/February 2019)

10. Review

Robert A. Schaut and W. Porter Weeks, "Historical Review of Glasses Used for Parenteral Packaging" July/August 2017

B. cepacia: What is it and Why is it a Concern?

Hospitals and Pharmaceutical Plants on the Prowl for this Uninvited Guest

Marc Baiget Francesch, Tiselab

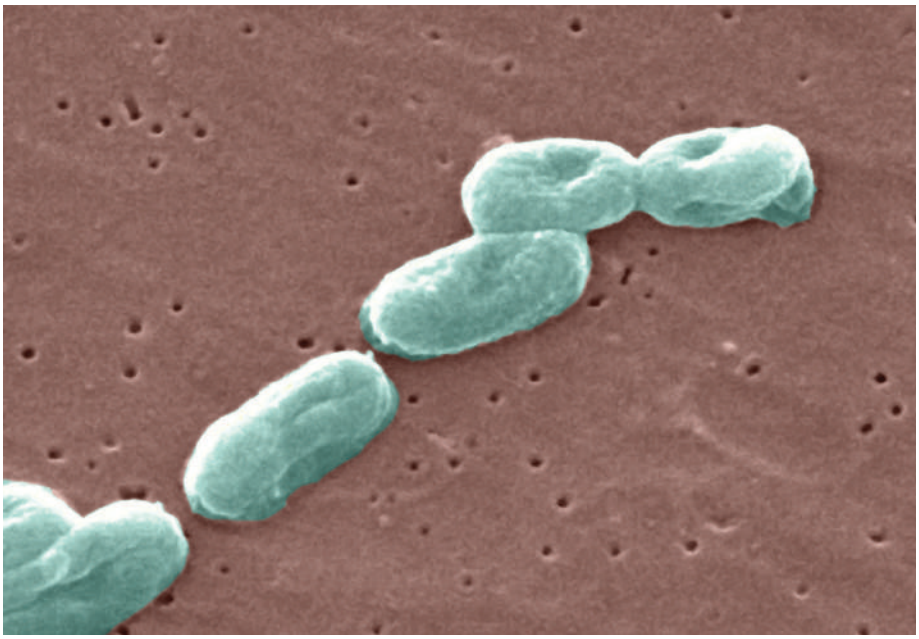
Burkholderia cepacia has been in the news…again!

Even though this pathogen is not a newcomer (one can easily find papers from the 1990s discussing its dangers), it continues to wreak havoc in pharmaceutical plants ***(1).*** Less than two years ago, two separate batches of oral solid medicine were found to be contaminated by *B. cepacia* ***(2–3)***. The year before, a manufacturer issued a Class I recall for saline flush IV syringes suspected to be responsible for *B. cepacia* bloodstream infections ***(4).*** A quick Web search shows these are not isolated cases. *B. cepacia* is a major contaminant in both sterile and nonsterile products. A review of U.S. FDA recall data from January 2012 to July 2012 found that 39% of contamination cases in nonsterile products were due to the presence of *B. cepacia*. ***(5)***

Before continuing, one might wonder, what is *B. cepacia*? *B. cepacia* is actually the name given to a group of Gram negative aerobic rod-shaped bacteria (*Burkholderia Cepacia* Complex or BCC). Despite living mainly in aerobic environments, those bacteria can survive in hypoxic conditions and possess the ability to grow in low nutrient media as well. This microorganism is generally harmless to healthy individuals but acts as an opportunistic pathogen, presenting a potentially fatal danger to immunocompromised patients. A recent study performed in Severance Hospital at Yosei University College of Medicine in Korea found a mortality rate of 41% among individuals suffering of *B. cepacia*- induced bacteremia ***(6).*** This is a problematic issue as this pathogen is quite proficient at reaching sick individuals through two main channels: hospital fluids and contaminated pharmaceutical products ***(7).***

A Hardy, Vicious Microorganism

There is another feature of *B. cepacia* worth to highlight, and this is its proficiency at developing a biofilm matrix.



Biofilm forming organisms feature a wide range of bacteria, including mainly Gram negative but also Gram positive pathogens ***(8,9).*** These microorganisms are generally quite hardy since the biofilm acts as a net that stops antibiotics from penetrating into the actual bacterial cell, exposing only the planktonic cells outside the matrix. ***(10).*** For this reason, bacteria communities that form biofilms show a higher than average resistance to antibiotics, stress and many other conditions that are usually detrimental to cells ***(11).*** All in all, it makes dealing with biofilm-forming bacteria difficult, especially those inside an individual's body.

A famous example of a biofilm related disease would be cystic fibrosis, which is mainly caused by *Pseudomonas aeruginosa* —a bacterium with a long, well-known association with *B. cepacia* (in fact, *B. cepacia* was initially known as *Pseudomonas cepacia*) ***(12).*** Even though changes in antibiotic administration patterns (like alternate antibiotic cycles or combined antibiotics administration) can significantly reduce its mortality, many biofilm infections are considered chronic, as a complete elimination of the pathogen from the host is very difficult. This, coupled with the great difficulty in detecting it via conventional methods, makes it a really unpleasant microorganism to deal with. Naturally, limiting its chances to reach the hospitals is vital to avoid a problem that presents huge human and economic costs.

Manufacturers Fight *B. cepacia*

But it is not only hospitals that are involved in this crusade against *B. cepacia.* Pharmaceutical companies have also a huge interest in eradicating this pathogen from their facilities, as its very presence forces production to stop, risking potential loss of clients, and even causing severe economic losses in some cases. As mentioned before, fighting a biofilm-inducing bacterium inside a human host can be a complicated task. Yet eradicating its presence in a plant's water systems might not be as difficult. Fortunately, the industrial environment allows for use of more aggressive methods and chemicals. Some new products have been appearing on the market, offering potential solutions that are more efficeint solutions than conventional bactericides. Many scientific teams are focusing on new approaches to eradicate *B.cepacia*, ***(13).*** Still, present solutions

have, so far, failed at eliminating *B. cepacia* completely from both infected humans and industrial water conducts.

Two-Front Approach to *B. cepacia*

Risk management of *B. cepacia* contamination can be tackled from two different perspectives. There is the hospiral approach, which focuses on good hygiene and patient segregation based on their microbiological status, and there is the industrial approach, which is based on detecting this microorganism efficiently enough to avoid contaminated products reaching the market.

Detecting *B. cepacia* presence is a hard task. *B. cepacia* is a bacterium that usually presents slow growth and many times remains undetected until it is too late ***(14,15).*** USP considered this matter critical enough as to dedicate a general chapter—which is currently undergoing an In-Process Revision—featuring tests for growth promoting, indicative and inhibitory properties of the media and a list of recommended media for the tests, and clues for the interpretation of possible *Burkholderia cepacia* colonies ***(16).*** In addition, some newer techniques like real-time polymerase chain reaction are being used in order to speed up the detection process. ***(17).*** It is also true, however, that these techniques, while being quicker than the traditional methods, are still relatively time consuming compared to others.

The development of an in situ media-independent device to detect *B. cepacia* in water (something similar to point-of-care devices in hospitals) could mean a big step toward better, quicker detection. Meanwhile, detection remains problematic. In order to lower the risks of *B. cepacia* spreading to the general public, it is recommendable to invest money on efficient detection systems for *B. cepacia* early detection. It is also highly advisable to thoroughly disinfect, especially in cases where *B. cepacia* or other biofilm forming bacteria have been spotted.

B. cepacia *is a bacterium that usually presents slow growth and many times remains undetected until it is too late*

Knowing the gravity of the situation, it might seem logical to think that *B. cepacia* should be considered a serious threat and be dealt with properly. In the end, tackling the problem at its source will save many lives and millions for both pharmaceutical plants and hospitals.

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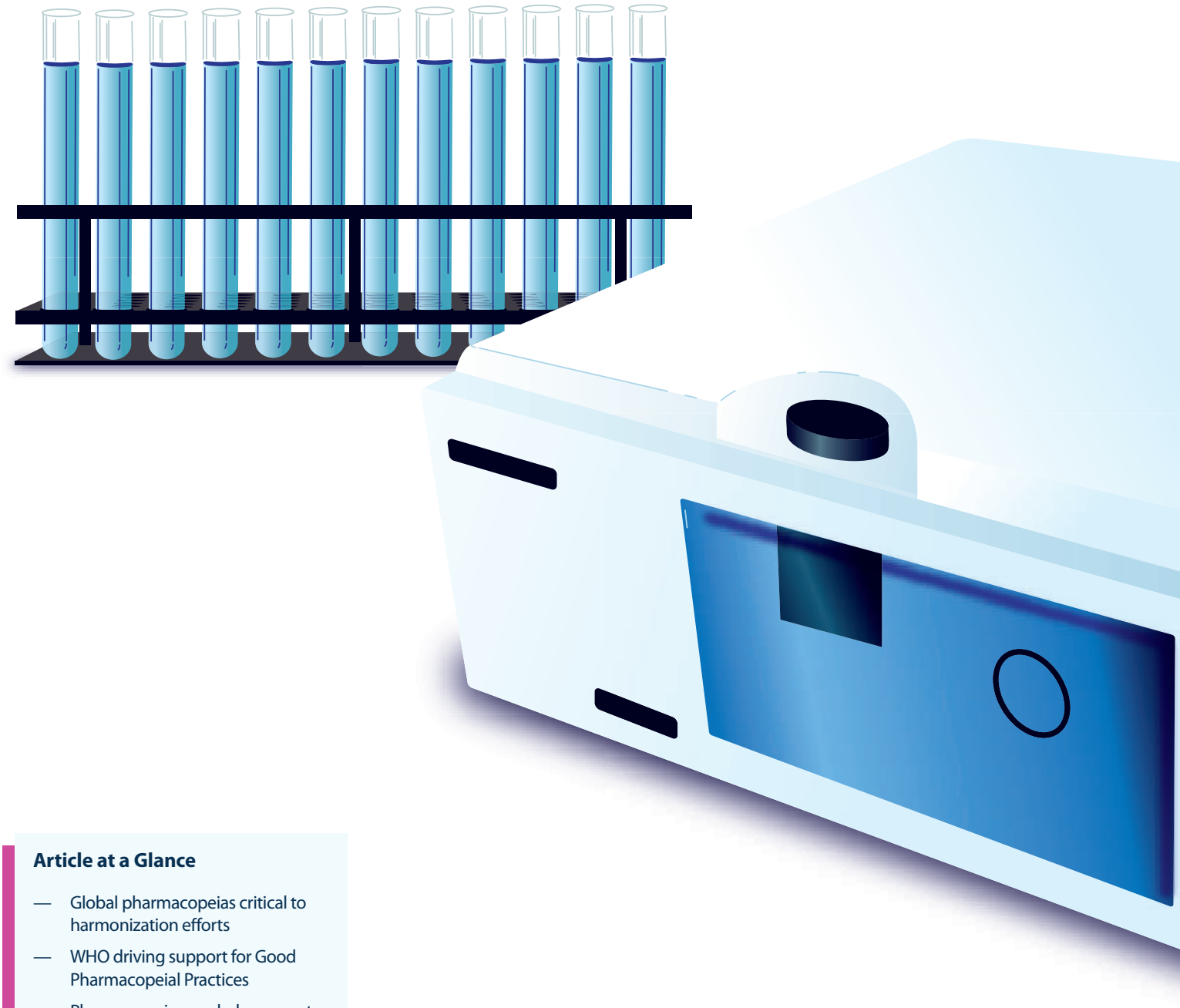

Article at a Glance

- Global pharmacopeias critical to harmonization efforts
- WHO driving support for Good Pharmacopeial Practices
- Pharmacopeias can help support innovation within pharma

IN THE 21ST CENTURY

Maintaining a comfortable state of health has always been a major human preoccupation. By the dawn of the first millennium, this was manifested in *De Materia Medica*, generally considered to be the earliest example of a pharmacopoeia. This treatise compiled contemporary tried and tested herbal and other remedies, methods for their preparation and their effects on patients. Fast forward two thousand years and the world has changed entirely and, with it, attitudes about health and well-being. Today, healthcare is dominated by a vast and powerful pharmaceutical industry that is closely regulated by an equally vast and powerful network of national and international legislation and guidance, including global pharmacopeias.

Yet the role played by pharmacopeias and the position they occupy in today's increasingly controlled environment is sometimes challenged. Have they outlived their usefulness? Do binding pharmacopeial standards result in duplication of efforts and additional strain on already heavily stretched resources? Does the sum of these regulations and standards serve to stifle innovation? Such criticisms as these, sometimes leveled at pharmacopeias worldwide, are addressed in this article.

With the health of a nation now seen as an indicator of successful development, healthcare and, by extension, pharmaceuticals are of increasing concern both to the population in general and to governments. Coupled with the rise in global trade is the pressure to ensure the sustainability of our healthcare systems. The need to produce medicines at the lowest possible cost without compromising their quality, safety and efficacy, as well as the need for a comprehensive regulatory framework governing this global industry has never been so clear. They make frequent appearances on international agendas. Local laws and regulations governing the pharmaceutical sector vary and evolve at different rates, and quality assurance levels may differ from country to country, but recent years have seen an emerging trend for harmonization that reflects the globalization of pharma.

Look at ICH, for example. It began as a tripartite organization (Europe, United States and Japan) in 1990, but now comprises members and observers from all over the world, reflecting the shift in the production of APIs and medicines to countries outside its initial membership. And, while these additional ICH members have their own regulatory frameworks under which locally based manufacturers are legally bound to operate, they may have adopted varying GMP systems. Notably, this means that surveillance and inspection of compliance may differ from that expected in Europe or the United States.

Today's pharmacopeias provide publicly available, common and legally enforceable quality standards for medicines and their components. As such, they complement and assist medicinal product licensing and inspections processes, making them one of the pillars supporting the public health structure worldwide. These monographs and general texts are developed in full transparency with the participation of the pharmaceutical industry, relevant national authorities and other associated stakeholders to ensure they are both authoritative and relevant. The involvement of manufacturers in the standards-setting process is crucial—it is through their knowledge and expertise that the test methods described remain robust and affordable. It would be unthinkable for any pharmacopeia today to disregard their input. At the same time, a strong alignment between the pharmacopeia and➤

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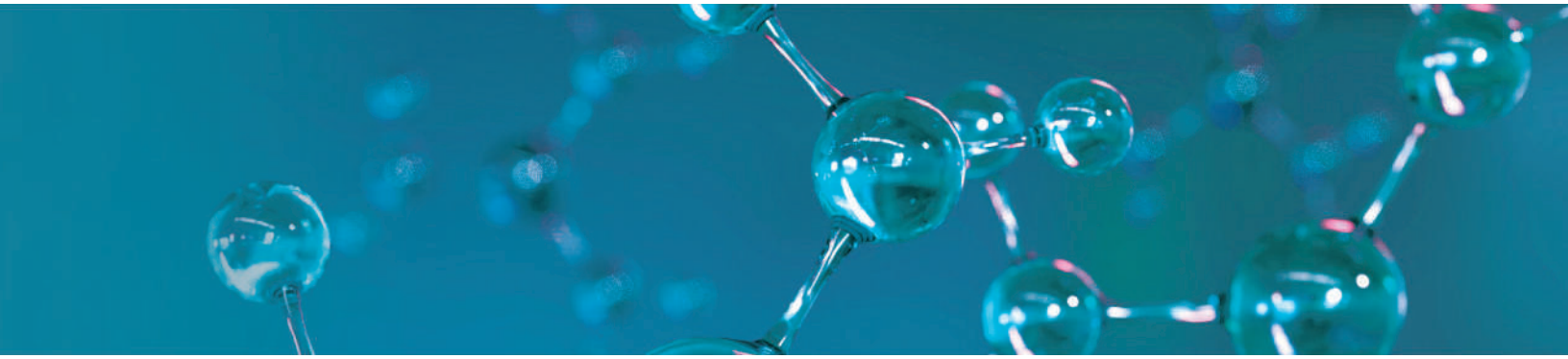

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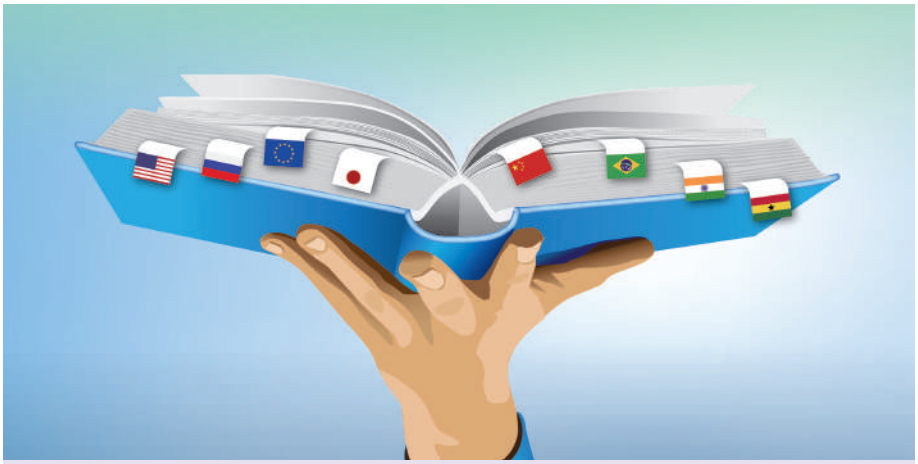
the regulator is of equal importance as it promotes compliance with pharmacopeial requirements and, by extension, ensures predictable outcomes of regulatory decisions. Pharmacopeial standards provide a shared understanding of suitable quality attributes for medicines and their components. By "speaking the same language" when referring to the necessary analytical methods that have to be applied as a "minimum standard," they do much to enhance the efficacy of communication between manufacturers and regulators. This helps speed the development of new medicines and, ultimately, their availability to the patients that need them.

The need for harmonization has also been felt by the pharmacopeias and several harmonization initiatives have been launched with a view to developing global standards that deal with the expansion in international trade. These include the work carried out by the Pharmacopoeial Discussion Group (PDG), traditionally focused on retrospective harmonization, and a number of bilateral or multilateral initiatives of individual pharmacopeias that primarily encompass prospective harmonization of pharmacopeial standards or adapt/adopt principles. More recently, and under the auspices of WHO, global pharmacopeias have drafted a guidance on Good Pharmacopoeial Practices for participating pharmacopeias. This information is intended to facilitate the appropriate design, development and maintenance of harmonized standards ***(1).*** Taking this "bottom up" approach, by agreeing on the general principles of standard development and lifecycle management, should encourage collaboration and closer ties among participating pharmacopoeias and foster further harmonization efforts. As an equal and unbiased partner to regulators on the one hand, and to industry on the other, pharmacopoeias provide a level playing field with clearly identified and acknowledged goalposts.

> **"investment in new treatments can only be successful in the context of an effective regulatory framework, not a regulatory straitjacket"**

The question of impact on innovation is of particular interest. The pharmaceutical industry is one of the largest R&D spenders, but investment in new treatments can only be successful in the context of an effective regulatory framework, not a regulatory straitjacket. By listening attentively to the needs of both regulators and industry and rapidly incorporating new technological advances, pharmacopeias can ensure that their content remains relevant and state-of-the-art and that their quality standards and methods are not only able to ensure the safety and efficacy of medicines but reflect advances in technology and science. This proactive course is matched by an ability to react swiftly to emerging challenges and with a large degree of flexibility (through alternative methods).

Although a high level of quality control results from today's manufacturing capabilities and the commitment of the regulatory authorities to public health, pharmacopeias still have an important role to play in the global marketplace. In addition, there is a growing tendency to view regulations and quality standards as enablers of innovation rather than a burdensome but necessary evil. The core mission of regulators and standards-setting organizations is, of course, to protect public health, but it is also their role to assist the pharmaceutical industry in the most comprehensive manner possible. While this is not always the smoothest of journeys, it ultimately benefits all stakeholders. Pharmacopeias continue to have a function that is neither duplicative of, nor incompatible with the global regulatory framework. Rather, they provide a benchmark for quality, underpinning the overall safety of medicines, and make a vital contribution to public health protection.



Interested in learning more about global pharmacopeias? Susanne Keitel will chair the second PDA Europe *Pharmacopoeia Conference,* May 16-17 in Geneva.

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Future Lies in Continuous Manufacturing Technology

But What Do the Global Regulators and Pharmacopeias Have to Say?

Bei Ma, Pinea Group

Pharmaceutical manufacturing has traditionally been seen as a manufacturing sector lagging behind in technological innovation. Due to its highly regulated nature and resource concerns, pharma manufacturers have been hesitant to disrupt everyday manufacturing operations to introduce new technologies.

According to a January 2019 report, the emerging technologies that characterize Industry 4.0—connectivity, advanced analytics, robotics and automation—have the potential to revolutionize every element of pharmaceutical manufacturing within the next five to ten years ***(1).***

In recent years, pharmaceutical manufacturing leaders have been exploring new and innovative technical solutions to achieve better quality, improve productivity and operational efficiency and increase process throughput and yields. Advancements in technologies such as digitalization, artificial intelligence, machine learning, 3-D printing, precision medicine, automation, and augmented and virtual reality will shape the future of pharma.

Continuous manufacturing has been one of the most promising trends. The U.S. FDA has actively promoted continuous manufacturing through both its Emerging Technology Team (one of the Team's cornerstone initiatives) and its draft guidance, *Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization Guidance for Industry* ***(2).*** The EMA also supports the advancement of technology but remains less active than FDA. Some European manufacturers have had continuous manufacturing in place for many years; thus, the technology is not as "hot" as it is in the United States and support from European regulators is more understated ***(2).***

Worldwide Support Builds for CM

Since 2014, three international symposia have been held on continuous manufacturing—two at the Massachusetts Institute of Technology (2014 and 2016), and most recently in London (October 2018). The first symposium, which focused primarily on small molecule production, resulted in a white paper on the regulatory and quality considerations that established a regulatory baseline for continuous manufacturing ***(3).*** The second, which split the discussion equally between small molecules and biologics, supported the need for a harmonized ICH guideline on the technical and regulatory aspects ***(3).*** And the third focused on case studies, business cases and supply chain impact in both the small molecule and biologics spaces ***(3).***

In November 2018, the ICH Management Committee endorsed the final business plan on a new proposed guideline, ICH Q13: *Continuous Manufacturing for Drug Substances and Drug Products*. This proposed quality guideline will harmonize continuous manufacturing-related definitions, articulate key scientific approaches for the technology and harmonize regulatory concepts and expectations ***(4).*** The new guideline will likely take three years to develop and finalize ***(5).*** Some 35 experts participate in the ICH Expert Working Group, among them representatives from ANVISA (Brazil), the European Commission, the U.S. FDA, Health Canada, HSA (Singapore), MFDS (Korea), MHLW/PMDA (Japan), NMPA (China), Swissmedic, TFDA (Taiwan), USP and others.

Among the leading pharmacopeias, USP has actively supported continuous manufacturing technology to reduce barriers to the adoption of continuous manufacturing technology. In the latest edition of the *Pharmacopoeial Forum*, USP published a Stimuli article on pharmaceutical continuous manufacturing that includes the sections "Definitions," "Material Properties and Characterization," "Risk Management, PAT and Statistical Tools" and "Regulatory Considerations" ***(6).*** Because the European, Japanese and Chinese pharmacopeias are part of their regional/national health and regulatory agencies, it is not surprising that general consensus has been achieved through their participation in the ICH Q13 Expert Working Group. This demonstrates that these compendia understand the potential continuous manufacturing offers for improving the efficiency, agility and flexibility of drug substance and drug product manufacturing.

While the UK MHRA has no official representation in ICH, the agency also

A breakout session at the May PDA Europe *Pharmacopoeia Conference* will explore pharmacopeial chapters on continuous manuacturing from a variety of compendia.

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sees possibilities continuous manufacturing poses. **Mike Birse,** Group Manager of Device Safety and Surveillance at MHRA, stated in an article for *In-Pharma Technologist* that MHRA has spent a great deal of time working with stakeholders: "We work with other stakeholders and other regulators internationally to try to smooth our approach, particularly in this space. There's a lot of work we've done across Europe and with the US FDA, in terms of going out to sites to see how the industry is implementing the process" ***(7).***

Stakeholders will want to closely monitor the development and progress of the new ICH Q13 guideline, as well as review and provide comments to the ICH Q13 Expert Working Group.

The final ICH Q13 guideline, no doubt, will help harmonize regulatory standards and increase the consistency in regulatory assessment and oversight across regions. Still, no individual manufacturer could successfully adopt continuous manufacturing technology on its own. Global collaboration among regulators, pharmacopeias, pharmaceutical industry, tech companies and other stakeholders remains central to ensure realization of continuous manufacturing.

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Bei Ma is the founder and CEO of the Pinea Group based in Washington, D.C. Previously, she served as Vice President of Global Healthcare and a key thought leader in Global Healthcare Sector for the British Standards Institution along with the U.S. Pharmacopeia.

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GROWTH PROMOTION TESTING FOR EM

Reference Materials Critical for Ensuring Effective Environmental Monitoring Tests

Brendan Tindall, biomerieux, and Graham Vesey, Regeneus

Growth promotion testing of culture media is an important part of microbiological testing in support of pharmaceutical quality ***(1).*** The growth promotion test is a quality control requirement that confirms the ability of a new batch of media to support growth of a predetermined selection of representative microorganisms. All media used in a cGMP facility should be tested, including media for microbial limits, environmental monitoring and sterility testing ***(2,3).*** Growth promotion testing requirements apply to in-house and externally purchased media ***(3,4).***

Suspension Method versus Reference Materials

Crucial to growth promotion testing are reference materials. Nowadays, microbiological reference materials are readily available from multiple suppliers, in all major locations and in many different formats, including qualitative and quantitative. Quantitative reference materials contain a defined number of viable microorganisms. They normally take the form of a freeze-dried or gel suspension, and are supplied with a Certificate of Analysis (COA) specifying the number of viable microorganisms that should be recoverable.

But before high-quality reference materials became available, growth promotion testing was usually performed by plating a serial-diluted microorganism suspension on both a new and a previously released media batch to compare recoveries. This method proved difficult in obtaining accurate results ***(5).*** This approach is also potentially flawed in that the inoculum does not come with a COA and a gradual decline in viability might not be readily detected. Testing with a reference material provides an independent and precise external calibration point. Every batch of ready-to-use reference material should come from an ISO 17034:2016-accredited manufacturer with a COA that offers quantitative data specific to the batch ***(6).*** The COA should also report a mean colony-forming-unit (cfu) count and the standard deviation for each batch.

Certified reference materials have been widely used in analytical chemistry for many decades but have only been available for microbiologists in recent years ***(7).*** A certified reference material is one characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that states the value of the specified property and its associated uncertainty of measurement, and a statement of metrological traceability ***(8).*** Metrological traceability is the property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty ***(9).*** Thus, when using a measurement result with metrological traceability, such as the average cfu count of a certified reference material accredited for its quantification, measurements can be meaningfully compared, even when they are made at different times and places by different people or using different equipment ***(10).*** For quantitative methods such as growth promotion testing, a certified reference material that has a quantitative property value, such as cfu, would further enhance the ability to achieve comparable results according to pharmacopeial requirements.

During pharmaceutical manufacturing, each facility must perform environmental monitoring that measures and monitors levels of microbial bioburden ***(11).*** Keep in mind that the pharmacopeias are not harmonized for environmental monitoring; each has varying requirements that demand very low initial contamination recovery rates or the detection of very low cfu levels (**Tables 1** and **2**). The requirements vary depending on the criticality of the manufacturing area to product sterility. Depending on the cleanroom classification, there can be very stringent requirements on the outcome of environmental monitoring. For example, in ISO 5 and 6 rooms, the cfu counts allowable are extremely low and need to be managed very closely. USP <1116> Microbiological Control and Monitoring of Aseptic Processing Environments states that suggested initial contamination recovery rates for aseptic environments in should only show contamination in control plates < 1% and < 3% of the times, respectively ***(12).*** That means at least 97% of the time, no growth is expected. Furthermore, the EU Guidelines to Good Manufacturing Practice, Annex 1: Manufacture of Sterile Medicinal Products is very clear about the cfu numbers recommended as limits of microbial contamination ***(13).***

For example, when considering contact plates for Grade A and B rooms (ISO 5 and 6), < 1 and < 5 colonies must be recovered. These very small numbers of cfu imply that the contact plates should be able to recover and grow a small number of microorganisms. Consequently, users must be confident about the quality, especially fertility performance, of the culture media used. Recent studies

Table 1 Suggested Initial Contamination Recovery Rates in Aseptic Environments Per 1116

Room Classification	Active Air Sample (%)	Settle Plate (9 cm) 4 h Exposure (%)	Contact Plate or Swab (%)	Glove or Garment (%)
Isolator/Closed RABS (ISO 5 or Better)	<0.1	<0.1	<0.1	<0.1
ISO 5	<1	<1	<1	<1
ISO 6	<3	<3	<3	<3

* All operators are aseptically gowned in these environments (with the exception of background environments for isolators). These recommendations do not apply to production areas for nonsterile products or other classified environments in which fully aseptic gowns are not donned.

Table 2 EU Guidelines in Annex 1

Recommended Limits for Microbial Contamination (a)				
Grade	air sample cfu/m^3	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	—
D	200	100	50	—

performed on environmental monitoring of surfaces have shown variation in the recovery of microorganisms between the surfaces sampled ***(14).*** Another study found discrepancies between the suppliers of contact plates, leading to random and systematic errors ***(15).*** These emphasize the importance of the performance and quality of the culture media used.

What Does USP Say?

USP growth promotion testing requirements for solid and liquid microbiological growth media is described in <61>:

"For solid media, growth obtained must not differ by a factor greater than 2 from the calculated value for a standardized inoculum. For a freshly prepared inoculum, growth of the microorganisms comparable to that previously obtained with a previously tested and approved batch of medium occurs. Liquid media are suitable if clearly visible growth of the microorganisms comparable to that previously obtained with a previously tested and approved batch of medium occurs" ***(1).***

USP also stipulates using less than 100 cfu. A factor of 2 is commonly interpreted as a recovery of 50% to 200%, otherwise, half or double the cfu count of the original growth promotion testing inoculum. In the case of growth promotion testing, this comparison is between the calculated cfu of the previously tested media and that of the new media batch. For example, if the previous batch of tested media had 50 cfu, the new media batch must have > 25 and < 100 cfu to pass. This approach allows between 25 and 100 cfu, which could be a variation of up to 75 cfu between agar plates, and still have a passing growth promotion testing result. This wide acceptance criteria allows for variation in the inoculum, particularly if the inoculum is prepared by serial dilution.

Unless monitored closely, comparing previous batches could result in a progressive decline in media performance, leading to the possible acceptance of less fertile culture media ***(16).*** For this reason, acceptance criteria that also include results based on a standardized microorganism preparation bring much more confidence to growth promotion testing results.

> "This wide acceptance criteria allows for variation in the inoculum"

Conclusion

- Use an ISO17034:2016-accredited reference material for growth promotion testing
- Choose a reference material or certified reference material with the smallest possible standard deviation to heighten the capability to observe media fertility changes
- Select a reference material or certified reference material with batch-to-batch consistency in cfu levels
- Ensure use of a reference material able to match COA quantitative data
- Compare the specified cfu count stated on that COA with the results from the growth promotion testing and set internal target recovery levels (nonselective media)
- Monitor trends in growth promotion testing results to look for discontinuities or drifts in media fertility over time

With the current availability of high quality, precise and accurate reference materials and certified reference materials, consistently accurate and precise results can be achieved to allow qualification of a new culture media batch's performance with a high degree of confidence.

[Editor's Note: The authors are part of the planning committee behind the inaugural PDA Europe *BioManufacturing Conference,* scheduled for Sept. 3–4 in Munich**.]**

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About the Authors

Brendan Tindall is the Global Solutions Manager and Program Director for BIOBALL at BioMerieux. He has worked in the healthcare industry for over 12 years in numerous positions and currently calls Japan home.

Graham Vesey is a co-founder of Regeneus and has served on the Board since incorporation. He was appointed Chief Scientific Officer in November 2014.

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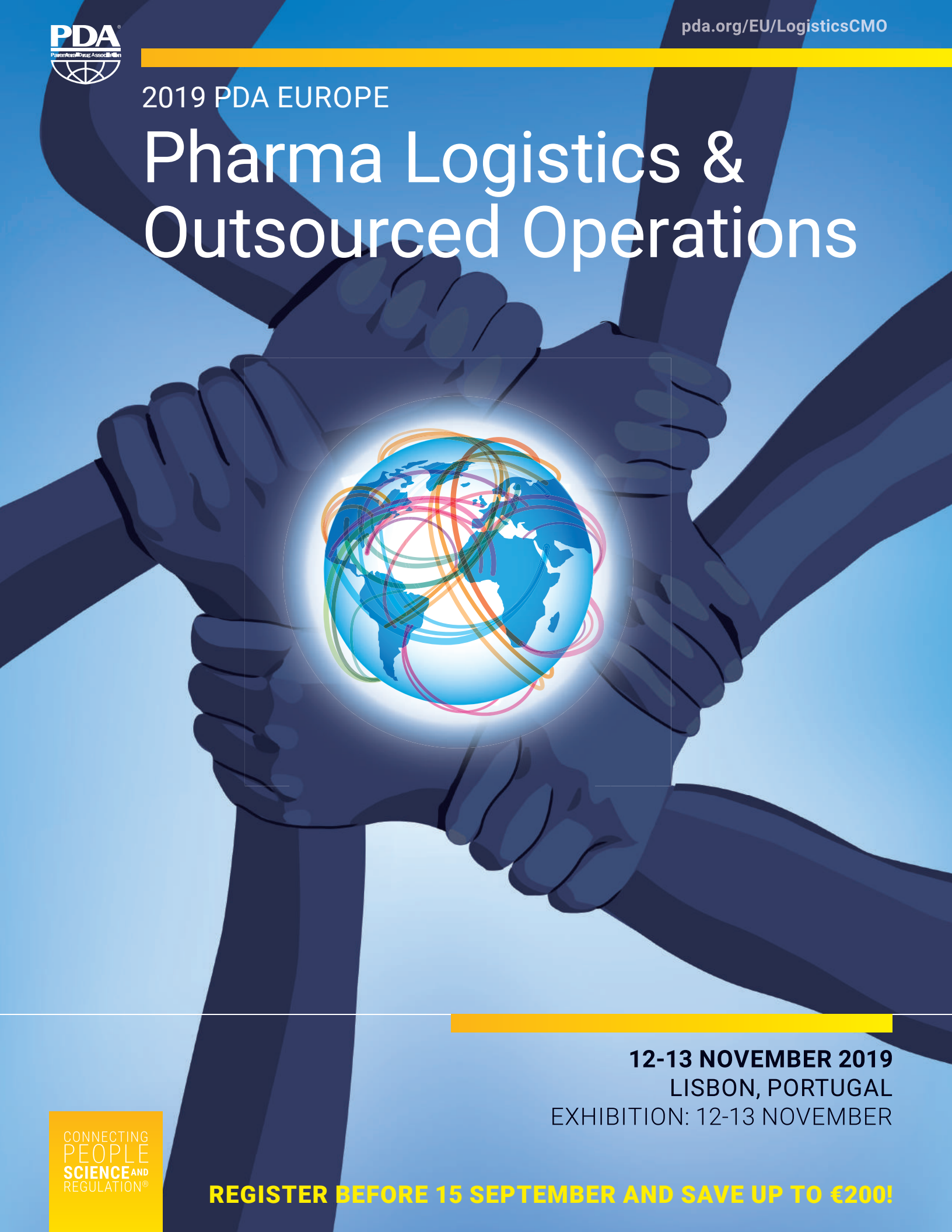

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Quality Systems Interest Group Expands Activities

Lothar Hartman, Managing Director, PhACT, and Chair of PDA Quality Systems Interest Group

Quality systems are a key element of any pharmaceutical operation. In light of significant recalls due to manufacturing issues, quality systems are more critical now than ever. Fortunately, PDA members have a resource to expand knowledge in this area: The Quality Systems Interest Group.

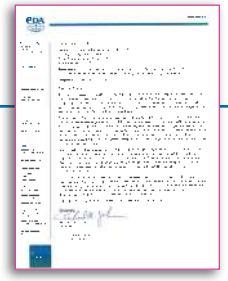
The Quality Systems Interest Group offers a forum for discussions on current topics and coverage of developments related to quality systems based off ICH Q10: *Pharmaceutical Quality System.*

The group's intention is to exchange information on the topic, share best practices, offer open discussion and develop practical approaches.

The group has grown tremendously since it was founded not that long ago. Currently, the group consists of the following 11 subgroups: management review, key performance indicators/metrics, continuous process verification, process owner, quality risk management, comparability of ICH Q10 with ISO standards, quality management systems auditing, quality manuals, knowledge management, training and documentation control.

For more information, please contact the chair of the group directly: lothar.hartmann@phact.ch

Clarity Needed on CMC Guidance for C&GT



December 6, 2018

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Reference: FDA Guidance for Industry Chemistry, Manufacturing, and Control Information for Human Gene Therapy Investigational New Drug Applications

Docket ID: FDA-2008-D-0205

Dear Sir/Madam:

PDA appreciates FDA's efforts to further clarify its thinking with respect to the content of the Chemistry, Manufacturing, and Control Information for Human Gene Therapy Investigational New Drug Applications. PDA further recommends this guidance include additional references to established regulatory guidance and pharmacopeial chapters that address topics specific to cell and gene therapy.

The scope of this document is unclear as it varies between describing the content and format of the material presented for INDs and a discussion of relevant GMP requirements. PDA proposes that the document be clarified against the intended scope. We recommend reorganizing the information or creating two separate documents to address the two topics. In its current form, the document is confusing and potentially in conflict with other guidances regarding GMPs for gene therapies and does not provide the appropriate focus on the respective topics.

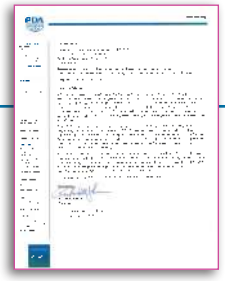
Additionally, further guidance on what is classified as drug substance (DS) vs drug product (DP) with respect to these products would be welcome, for example adding clarity around the use of the terms "DS" and/or "DP" for ex vivo modification of cells. For these types of therapies, the distinction of what is a drug substance and what is a drug product is often unclear. Please see the attached detailed comments for additional rationale and recommendations.

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 with experience in the practice of pharmacy as well as members representing our Biopharmaceutical Advisory Board and Board of Directors.

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

Sincerely,
Richard Johnson
President, PDA
Cc: Tina Morris, PhD, PDA
Josh Eaton, PDA

Proposed Change for RCR Language



December 6, 2018

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Reference: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up

Docket ID: FDA-1999-D-0081

Dear Sir/Madam:

PDA appreciates FDA's efforts to further clarify its thinking with respect to testing of retroviral vector-based human gene therapy products for replication competent retrovirus during product manufacture and patient follow-up. PDA commends the inclusion of the **Summary of revisions from the 2006 RCR Guidance** section to aid the audience in comprehension of the revised draft. Additionally, the removal of the need to collect and archive patient samples if RCR testing after 1 year provides negative results is a welcome modification.

The PDA does have one proposed change to submit relating to the draft language regarding the reduction or elimination of RCR testing of ex vivo genetically modified cells based on accumulated manufacturing and clinical data. PDA's recommendation is for the final guidance to provide **some indication as to how much data (i.e., number of supernatant lots or ex vivo transduced cells) would need to be provided to support the proposed reduction or elimination of testing.**

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 with experience in the practice of pharmacy as well as members representing our Biopharmaceutical Advisory Board and Board of Directors.

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

Sincerely,
Richard Johnson
President, PDA
Cc: Tina Morris, PhD, PDA
Josh Eaton, PDA

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Robert Lu, SolidBio
Nadine Ritter, Global Biotech Experts
Jacqueline Veivia-Panter, Legend Biotech
Li-Chun Wang, SolidBio
Martin Wisher, Merck KGaA
Keith Wonnacott, Pfizer

Published online first

Data Integrity Journey Has Only Just Begun

Jackie Veivia-Panter, Legend Biotech

> *"Data is a precious thing and will last longer than the systems themselves."* — **Tim Berners-Lee,** inventor of the World Wide Web

Hopefully all of us in the industry agree that our data is precious and requires the utmost level of integrity. Safe to say that we all agree that accomplishing this is much easier said than done. So where are you on your data integrity journey? Are you just beginning, somewhere in the middle or perhaps even have the end in sight? The concept of data integrity is not new, it has been an integral part of GMPs since conception…so why do we still have so many questions?

For most of us, the data integrity journey starts with a gap assessment and remediation effort. When we start remediation, we realize just how far and wide data integrity reaches and it can be quite overwhelming. As a result, many of us have started, stopped and redirected our path toward a more robust, holistic approach. Ensuring an understanding among our employees of what data integrity actually means is key to building a strong foundation.

As we transition from reactive to proactive, there are three areas that we need to discuss: quality culture, risk assessment and phase appropriate controls. As we build our foundation, we realize one key element will make or break our data integrity program—our quality culture. Does management understand and speak about data integrity? Do employees feel safe reporting data integrity issues? Is there even opportunity for doing such things? These, and many other cultural conditions, are a necessary part of the infrastructure needed to help data integrity programs succeed. A risk-based approach is also necessary to understand the criticality of data in a variety of settings, prioritize any CAPAs and meet regulatory expectations in as practical a manner as possible. Most companies start by addressing gaps found in the lab since the data generated there is critical and readily interpretable toward the quality of the product, but then what? Manufacturing? Supply chain and distribution data? Post-market surveillance?

Fortunately, there is a place to seek some answers and share best practices. Attend the *2019 PDA Data Integrity Workshop* this September in Washington, D.C. to hear industry and regulatory speakers. In addition, there will be panel Q&A for each session which will include multiple industry and regulator panelists. Come join us, set a course for your own journey, and help define the future of data integrity!

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Deep Dive into Biosimilars Continues

2018 PDA Biosimilars Workshop Outlines Global Regulators' Expectations

Stephan Krause, AstraZeneca, Emanuela Lacana, U.S. FDA, and Rebecca Stauffer, PDA

The *2018 PDA Biosimilars Workshop* held in Washington, D.C. last September provided an opportunity for further discussion on the topic of biosimilars, enabling industry representatives, academics and global regulators to convene around an increasingly critical topic.

The first session featured perspectives from global regulators on challenges encountered with submission of biosimilar marketing applications. Their presentations focused primarily on issues around manufacturing development, commercial production, and control strategies.

Emanuela Lacana, PhD, Associate Director for Biosimilar and Biologics Policy, CDER, U.S. FDA, started the session with an insight into challenges with achieving a first round BLA approval. These include analytical similarity, control strategy and routine manufacturing. For analytical similarity, inadequate reference standard qualification and characterization of critical attributes (e.g., impurities that affect potency, glycan structures, etc.) are common problems. She reminded attendees that qualified reference standards are critical for analytical similarity assessment and release of biosimilar product lots.

Martijn van der Plas, Senior Assessor Quality of Biological Medicines, Dutch Medicines Evaluation Board, then shared EMA expectations for biosimilarity. Biosimilar product development usually involves about 30 lots of reference product, compared to about ten lots for biosimilar product. In the case of biosimilarity, however, lot independence is not always guaranteed. Acceptance criteria for analytical similarity should be predefined, although applications frequently apply post hoc justification. It is recognized that criteria for comparability remain challenging and that there is currently no EU guidance defining expectations. Next, **Chantal Depatie**, PhD, Senior Biologist, Health Canada, indicated that a revised guidance on biosimilarity was released in December 2016 to reflect experience gained by Health Canada. Depatie suggested biosimilar sponsors provide a justification for a non-Canadian sourced version of the reference product as a proxy for the Canadian drug in comparative studies.

Following these three speakers, a panel discussion raised a number of points of concern. First, how does the biosimilar specification setting process compare to a traditional approach for innovator products? The panel pointed out that since clinical study lots are limited, it might be acceptable to rely on some clinical reference product data for some attributes, provided similarity is appropriately demonstrated. It is important not to miss attributes which require attention. The panel's recommendation is not to limit the number of critical quality attribute (CQA) assessments. They suggested developing a meaningful classification system and evaluate high and low criticality attributes using different criteria, rather than trying to get rid of CQAs. Some attributes might be linked to each other and it is important to assess them in this context.

Per the panel, it might also be acceptable to pool different reference product presentations for the similarity assessment, if appropriate risk assessments are performed on significant potential differences resulting from drug product manufacturing.

Other questions directed to the problem include the following (panel responses are below):

How are nominal versus label claim differences in protein content currently viewed?

It is a serious problem, and it happens. There have been precedents, notably concerning differences in clinical study outcomes when the label concentration was used for clinical studies as opposed to measured concentration.

How are differences observed in forced degradation studies to be interpreted?

If there are differences, they must be explained, according to the panelists.

Why is there a concern regarding a "binary" CQA /non-CQA definition, if risk assessment system is providing additional granularity?

Different "colors" and "shades" are important. In the context of similarity, there has been some confusion between how the criticality assessment is done for similarity as compared to the control strategy. Assessment of criticality should be conducted based on what is known about the product's attributes. Tiering approach for similarity is related to the statistical method and was not intended to have a direct connection to criticality of the attributes.

Was there ever a situation when a biosimilar product used a similar or even wider specification than the innovator product?

Usually knowledge of the reference product is not used for this purpose. Biosimilar specifications are usually set with clinical and manufacturing information from the biosimilar product.

FDA Hones in on Data Quality

The second session, moderated by **Christopher Downey**, Review Chief, CDER, FDA, addressed high-level technical challenges and how to avoid pitfalls frequently encountered during biosimilar candidate development, including data quality expectations, the creation of the final control strategy and strategic choices necessary for candidate selection and development. **Jee Chung,** PhD, Biologist, CDER, FDA, summarized current data quality concerns for analytical methods and preapproval inspections. For analytical methods, she emphasized criticality for suitable method

qualification, validation and transfer. She explained the importance of reference standard qualification. Further, the Agency has had concerns regarding interpretation of analytical similarity whenever multiple different reference standards are used during analytical similarity testing.

Next, **Catherine Srebalus Barnes**, Pfizer, provided detailed information on development processes for biosimilars. The best overall approach for biosimilar product development is to draft the CQA assessment first then refine it later. Additional major considerations and/or suggestions

For the procurement of reference product lots, she recommends that sponsors sample fewer lots over a longer time period rather than acquiring a large number of lots in a limited time frame. A formal prospective procurement plan and testing strategy is recommended. Specifications can be derived from reference product results for end of shelf life. When wider limits are used versus analytical similarity results, regulators expect tight controls.

Following this session, audience members had a number of questions for the speakers. For one, is a final analytical similarity assessment post-PPQ a common practice? Not necessarily, concurred the panelists, but PPQ lots should be included as final and representative material. Further, the FDA representatives stated that specifications are set at a certain timepoint. Things can change based on a new indication. It is not only about testing the reference product range. Sponsors should not automatically assume/use this argument.

A long and intense discussion then followed on 21CFR part 11 compliance expectations for characterization testing data. The FDA panelists reiterated that analytical similarity replaces a portion of the clinical data, therefore, expectations for data fidelity/integrity are also relatively high for characterization results. Thus, it is important to understand the role of different datasets and to assess any potential issues with data integrity in non-GMP laboratories as FDA has concerns that data may otherwise not be accurate and complete. 21CFR Part 11 is important here because clinical studies are reduced for biosimilars compared to innovator drugs and the analytical similarity assessment carries a great deal of weight in the overall similarity assessment.

Sponsors should therefore consider all aspects of the available data and for the basis of the reference product range (e.g., process variability versus unintended shift). Sponsors should assess whether it might be appropriate to establish a specification and a control range (to assure OOT results would be appropriately investigated).

Barnes suggested for post-approval comparability to first use ICH Q5E: *Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process* together ("hybrid" approach) with applying relevant analytical similarity data. **Barbara Rellahan,** PhD, Director, Product Quality (Biosimilars), Amgen replied that her company has not included any data for analytical similarity for post-approval changes (no reference product data included). Lacana commented that in the absence of current FDA guidance, FDA cannot comment at this point of time. She suggested that sponsors should consult with FDA for major changes until a guidance becomes available. **Marjorie Shapiro,** Chief, Laboratory of Molecular and Development Immunology, PhD, FDA, reminded participants that a draft guidance on post-approval changes for biologics is planned publication this year. Theoretically, the reference product and bioimilar remains linked, connected via the Q5E change sequence through post-approval changes.

In the closing Q&A, numerous topics came up for discussion.

Do we have a common vision of the role of statistical tools in the demonstration of similarity?

The consensus among panelists was that statistics should not be used alone in making an assessment for analytical similarity. Statistics are supportive but not necessarily decisive.

In addition, the signal-to-noise ratio ("sensitivity") is critical for deciding whether an attribute is equal or different and a confidence interval for a specific signal/difference should describe the level of certainty/uncertainty. An appropriate sample size should be used to obtain the desired confidence level in the results to be compared. For the criteria for equivalence tests, panelists agreed that the acceptance criteria should ideally reflect a practical significance.

What will be a direction for EU? Will there be a formal guidance outlining these challenges?

Currently, Van Der Plas, explained that the European Union is not ready for prescriptive guidance, but this approach can change, if for example, pharmacovigilance data show new signals.

Of course, there was much more Q&A, enough to fill several volumes! For this reason, the organizers of the *2018 PDA Biosimilars Workshop* invite interested parties to consider attending the *2019 PDA Biosimilars and Vaccines Conference.* All of these meetings have proven to be fruitful opportunities for discussion and the organizers plan to consolidate this material into other publications and extended articles. PDA's biosimilars conferences and workshops remain a way for those interested in the latest regulatory expectations for these innovative products to remain in the loop.

About the Authors

Stephan Krause, PhD, is AstraZeneca's Director of QA Technology. He manages the global biologics control strategy steering committee. He is also the coleader of PDA's Biosimilar Initiative.

Emanuela Lacana, PhD, is currently the Associate Director for Biosimilars and Biologics Policy in the Office of Biotechnology Products in CDER. Prior to her appointment at the FDA, she worked at Georgetown University and at NIH.

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Advancing Cell and Gene Therapies

Michael Blackton, Adaptimmune

"In contrast to traditional drug review, where 80 percent of the review is focused on the clinical portion of that process, and maybe 20 percent is focused on the product issues, I'd say that this general principal is almost completely inverted when it comes to cell and gene therapy." **— Scott Gottlieb,** Outgoing U.S. FDA Commissioner

Cell and gene therapies are one of the most promising areas in healthcare. These innovative therapies have the potential to radically change patient outcomes in diseases where there is often no available therapy. Recently in the United States, we have seen the U.S. FDA approve two cell therapies and a gene therapy product. According to the FDA, in the United States, there are over 800 active INDs, and it is expected that by 2020 we will see well over 1000 active INDs, and by 2025, an estimated ten to 12 cell and gene therapy products gaining approval! In Europe and the rest of the world, advanced therapies are experiencing a similar trajectory. Because these products involve complex manufacturing processes and require advanced regulatory strategies to navigate the pathway toward approval, PDA is in a unique position to advance understanding in this area.

A few areas where the PDA has brought value to our members and the industry include:

1. **Cell and Gene Therapy Conferences.** PDA has hosted three meetings in the United States with a singular focus on driving collaboration between industry and regulators with discussion topics covering cutting edge science, analytical methods development, GMP compliance, manufacturing/supply chain challenges, and regulatory expectations. In Europe, the annual *Advanced Therapy Medicinal Products* conference has been active for a number of years, with programs touching on similar issues but with an emphasis on European requirements. The *2019 Cell and Gene Therapy Conference* takes place May 6–7, in Long Beach, Calif., and in Europe, the 2019 *Advanced Therapy Medicinal Products* conference will be held June 4–5 in Vilnius, Lithuania.

2. **Technical Reports.** With the release of *Technical Report No. 81: Cell-Based Therapy Control Strategy* earlier this year, PDA continues to actively advance the science of product realization for cell and gene therapies, in particular, the concepts of target product profile (TPP), quality target product profile (QTPP) and control strategy as applied to cell therapies. This year we expect more proposals for technical reports that will be focused specifically on moving advanced therapies through development into the market.

3. **Cell and Gene Therapy Interest Group.** In late 2017, PDA established the Cell and Gene Therapy Interest Group to drive collaboration among professionals in the field and to better define industry best practices for cell and gene therapies. At the *2019 PDA Annual Meeting,* the interest group teamed up with the Quality Risk Management Interest Group to offer two compelling presentations outlining how quality risk management is used for cell and gene therapies. Watch for more interest group meetings at PDA conferences in 2019.

4. **Standards Development.** This year, PDA, as an accredited ASTM standards organization, began working to develop a standard for the cryopreservation of cells. This is an immensely important document that will help those developing cell therapies with standard terminology and technical requirements for cryopreserving their products.

As we move through 2019 and beyond, PDA will continue to advance understanding of cell and gene therapies, and I encourage members to learn more about these initiatives. Please visit the PDA website for more information.

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