People • Science • Regulation

PDA Letter

Volume LIV • Issue 10 www.pda.org/pdaletter November/December 2018

FDA's ORA Realignment, MRA, NIPP, Concept of Operations:

How it All Fits Together

28

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November/December 2018 PDA Letter

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FDA's ORA Realignment, MRA, NIPP, Concept of Operations:

How it All Fits Together

Rebecca Stauffer, PDA

Just over a year ago, the U.S. FDA released detailed information about the restructuring of the newly realigned Office of Regulatory Affairs (ORA). **Alonza Cruse,** Director, Office of Pharmaceutical Quality Operations, ORA, provided an update on this and other ORA initiatives on Sept. 24 in the second plenary of the *2018 PDA/FDA Joint Regulatory Conference.*

Cover Art Illustrated by Karol Keane

Process, Interrupted

The Effect of Gamma Irradiation Process Interruption on Microbial Resistance of *G. stearothermophilus*

Fatima Hasanain, Polymer Materials Specialist, Nordion (Canada) Inc.

Sterilization process monitoring and control is key to product safety in the pharma industry. ISO/AAMI 11137-1 addresses the importance of monitoring radiation process parameters to ensure products have been processed according to specification. Radiation sterilization standards generally state that any doses delivered to product are cumulative.

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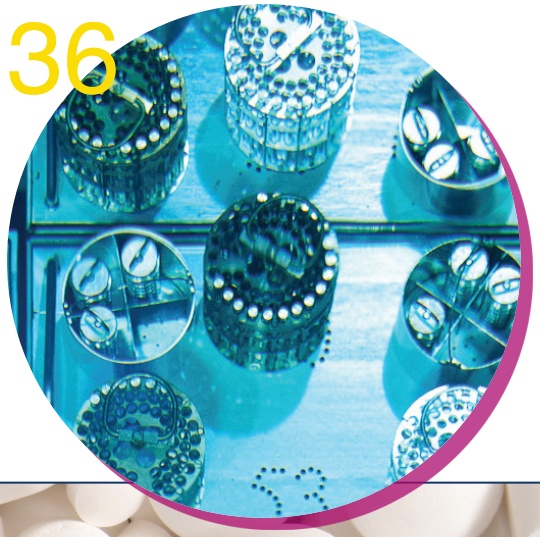

Hidden Contamination in Starting Materials

Are Your APIs Free of Dirt?

Annette Kirsch, PhD, Merck KGaA

Contamination by foreign particles has only been covered to a small extent in regulatory and compendial guidelines and, even then, mostly for parenteral products. The European Pharmacopoeia only covers particle contamination of oral herbal medicines. To cover this gap, the Active Pharmaceutical Ingredients Committee (APIC) and the International Pharmaceutical Excipients Council (IPEC) published position papers in 2015 explaining how pharmaceutical manufacturers should deal with particles in APIs and excipients.

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InfoGraphic

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Annex 1: Are You Prepared?

The EU Annex 1 revision is currently in draft form. Is your company ready for the final version?

Interactive

PDA Letter

Volume LIV • Issue 10 www.pda.org/pdaletter

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

Articles published in the PDA Letter do not represent the official positions of PDA, Inc., but are the opinions of the authors submitting the articles.

Subscriptions are not available.

Articles published in the PDA Letter do not represent the official positions of PDA, Inc., but are the opinions of the authors submitting the articles.

Departments

Digital Exclusives

> **On the Issue** | Audit Trails
Novartis' **Christian Scheidl** discusses the role of audit trails for ensuring data integrity at the 3rd PDA Europe Annual Meeting.

> Future Challenges in Visual Inspection Processes
Warning letters for visual inspection issues may have gone down but some issues remain.

> Standing Guard
A comparison of the standard LAL assay with alternative methods.

pda.org/letter

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pda.org/2019BiopharmWeek

Share Your Leading-Edge Research on Biopharmaceuticals!

PDA Parenteral Drug Association

Abstracts are currently being accepted for oral or poster presentations at the *2019 PDA Biopharmaceuticals Week*! Take advantage of this new week-long event format featuring three exciting meetings focused on aspects of Biopharmaceuticals. Submit an abstract today to showcase your work in this evolving area! Case studies are particularly desired.

Topics of interest include, but are not limited to:

- Biopharmaceutical manufacturing and controls
- Cell and gene therapy product integrity and delivery
- Vaccine development and manufacturing
- Virus safety and development

See the complete list of suggested topics and submit your abstract by **December 7** at pda.org/2019BiopharmWeekCFA

Learn more at pda.org/2019BiopharmWeek

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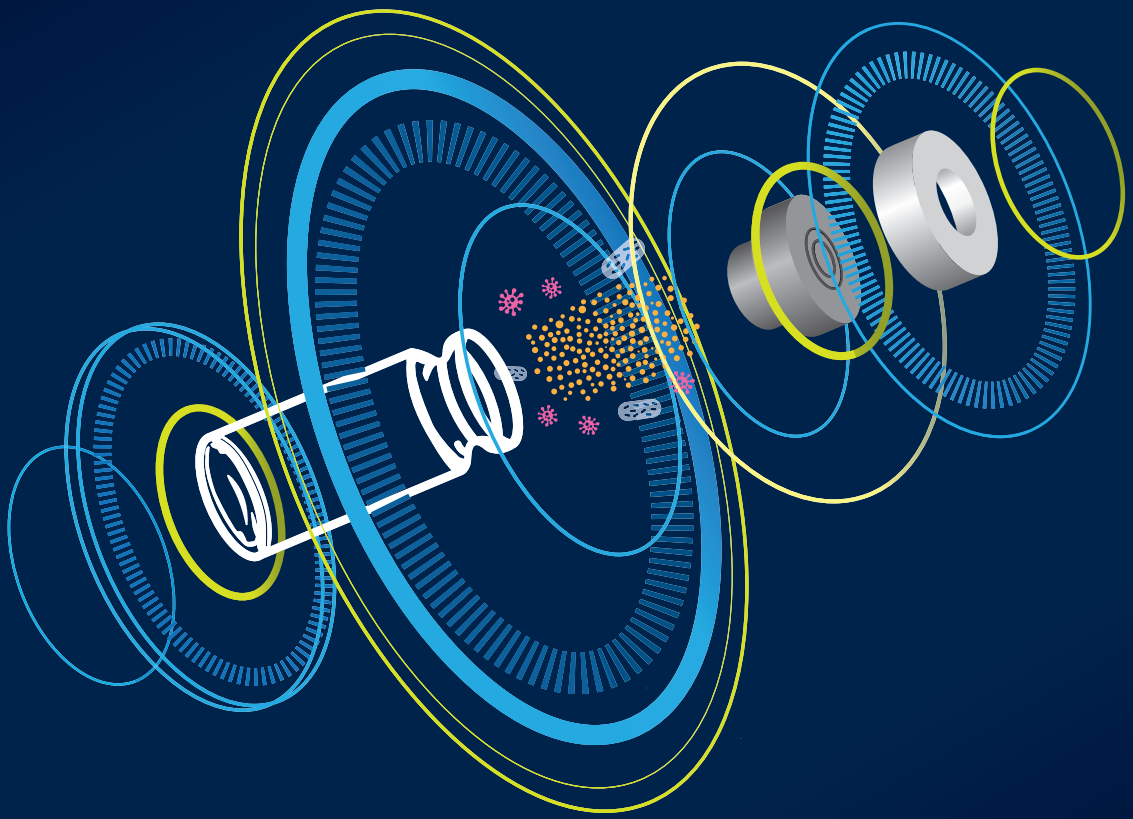
pda.org/eu/parpack2019

2019 PDA EUROPE

Parenteral Packaging

Interaction of Product, Package, and Process



19-20 MARCH 2019
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Closing Out an Exciting Year

I am not a fan of clichés. At the same time, I cannot help but say, "Wow! 2018 went by fast." Most of us have heard someone utter some variation on this theme at the end of every year. That said, cliché or not, it does feel like 2018 went by fast, and probably because the year was filled with many innovations and firsts for the *PDA Letter.*

We enjoyed great success with our On the Issue video series. In January, we filmed Corning's **Timothy Hunt** on location at the *2018 PDA Glass Quality Conference* in Washington, D.C., for the first of nine "On the Issue" videos we produced in 2018—a record number (so far). Our on-location shoots continued throughout the year with stops in Orlando (Annual Meeting), Berlin (PDA EU Annual Meeting), North Bethesda (PDA Pharmaceutical Microbiology Conference), and PDA's own Training and Research Institute. While these locations offered excellent backdrops to our videos, it was our repeat visits to the U.S. FDA Headquarters that were truly exciting. For the first time, but hopefully not last, we had the opportunity to interview FDA officials (CDER's **Dan Mellon** and **Francis Godwin**) for On the Issue videos. Another first was using guest-interviewer, PDA Board member **Masahiro Akimoto,** to discuss continuous manufacturing with Japan PMDA official **Issei Takayama.** Not only was he was the first regulator we filmed but this was the first non-English video we produced.

If you have yet to see an On the Issue Video, the entire series can be accessed on the PDA YouTube Channel and on the *PDA Letter* website: www.pda.org/pda-letter-portal/multimedia/videos.

In March, we posted a summary of the *2017 PDA Container Closure, Devices and Delivery Systems: Compatibility and Material Safety Workshop* (www.pda.org/pda-letter-portal/awareness-critical-for-container-closure-components), an online feature story that includes images, charts and tables presented at the workshop. The moderators of each workshop session extracted the highlights and key messages of those discussions. Special thanks to *PDA Journal of Pharmaceutical Science and Technology* editor **Rich Levy** and PDA webmaster **Faramarz Kolivand** for their assistance in making this happen. We are currently working on a similar, online-only summary of this year's *Vaccines* conference held in Málaga, Spain, which should publish before Dec. 31.

In addition to videos, conference summaries and our regular issues, the *PDA Letter* website has a lot to offer. In 2018, we published 13 "online-only" articles (these do not appear in the printed Letter), which was a record since the new *PDA Letter* portal launched two years ago. We also publish selected Letter articles ahead of print. I encourage readers to check out the Letter site frequently to see what is new. At least one new piece of content (i.e., article, video, infographic) is posted each week.

This issue offers another PDA first: an interactive infographic. The draft Annex 1 revision remains a hot topic, and we would like to learn who is getting ready and how. Scan the barcode in the *PDA Letter* InfoGraphic on page 42 to take a short, anonymous survey about Annex 1 preparedness. The results will be used to create a follow-up infographic.

Throughout the year, I hear from members about the *PDA Letter* and find it fascinating to learn how folks use it, where and when they read it, and what we can do to make it a strong industry resource. As always, I welcome your feedback, input and recommendations. Catch me at a PDA conference or send me an email (stauffer@pda.org). And, if a particular article has encouraged you to try something new at your company, I would love for you to share it with me in a "Letter to the Editor."

All in all, it has been a busy 2018 for the Letter staff...and the year is not yet over! We continue to try new ways to enhance our content for your benefit and fully expect that 2019 will be busier and better still.

Rebecca Stauffer

2018 Saw New Editorial Team for Journal, Pharma Glass Collection

Walter Morris

The highlight of 2018 for PDA's publishing activities was the appointment of a new editor for the *PDA Journal of Pharmaceutical Science and Technology:* **Rich Levy.** Many PDA members are already familiar with Dr. Levy. For 13 years he served as PDA's Senior Vice President of Scientific and Regulatory Affairs. Anyone who has volunteered on an advisory board, a technical report team, a regulatory commenting task force or a program committee can tell you Dr. Levy is committed to the highest standards of excellence in PDA's publications and comments.

Dr. Levy is not only charged with continuing to publish research/technology manuscripts of interest to the PDA community, but with creating a volunteer editorial board to increase opportunities for PDA's growing membership to get involved with the PDA Journal. He is already sorting through dozens of interested volunteers, and we hope to have the new PDA Journal Editorial Board in place by early 2019.

The Journal factored into three other publishing highlights in 2018:

- *PDA Technical Series: Pharmaceutical Glass*
- *2017 Viral Clearance Symposium* proceedings
- "The Impact of Quality Culture on Operational Performance—An Empirical Study from the Pharmaceutical Industry" (Quality Culture Assessment), a collaborative effort between PDA and the University of St. Gallen.

The Technical Series, a collection of 19 articles relating to pharmaceutical glass published in the PDA Journal over the last decade, was made available in the PDA Bookstore (www.pda.org/bookstore) in March. In April, as part of its PDA Research series, PDA published the results of the *2017 PDA Glass Quality Survey*. These popular books are available to PDA members at a special member rate.

And, of course, PDA technical reports play an important part in our 2018 publishing activities, including four new reports:

- *Technical Report No. 79: Particulate Matter Control in Difficult to Inspect Parenterals*
- *Technical Report No. 80: Data Integrity Management System for Pharmaceutical Laboratories*
- *Technical Report No. 81: Low Endotoxin Recovery* (anticipated)
- *Technical Report No. 82: Cell and Gene Therapy* (anticipated)

In 2019, I look forward to meeting the new PDA Journal Editorial Board, issuing more PDA technical series and research publications and producing many more PDA technical reports.

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pda.org/EU/Annual2019

4th PDA Europe Annual Meeting

25-26 JUNE 2019
AMSTERDAM, THE NETHERLANDS
EXHIBITION: 25-26 JUNE
EDUCATION & TRAINING: 27-28 JUNE

MARK YOUR CALENDAR

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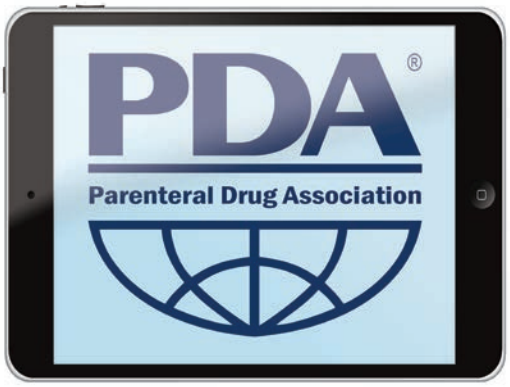
PDA In the News

Below is a sampling of articles that have mentioned PDA in the past few months.



American Pharmaceutical Review
September 26, 2018
"Calculating Endotoxin Limits for Drug Products"
— **Karen Zink McCullough**
tinyurl.com/y7787o6x

Healthcare Packaging
September 24, 2018
"Live from PDA/FDA: Considerations for Connected Autoinjectors"
— **Keren Sookne**
tinyurl.com/y9hawqfe

Maas & Peither
September 12, 2018
"Regulatory Update at the PDA European Annual Meeting: A report on the PDA European Annual Meeting 2018 – Part 2"
— **Thomas Peither**
tinyurl.com/y8zgj4ce

Pharmaceutical Manufacturing
July 19, 2018
"Empty Chamber Studies (aka Much Ado About Nothing): Recommendations for executing empty chamber studies for sterilization qualification/validation"
— **James Agalloco**
tinyurl.com/y95ulrq5

Pink Sheet
October 5, 2018
"FDA Compliance Experts Advise Against Treating Minor Changes As 'Planned Deviations' "
— **Bowman Cox**

Pink Sheet
October 16, 2018
"EMA Aims To Carry On With EU GMP Annex 1 Revision Despite Brexit-Related Staff Departures"
— **Joanne S. Eglovitch**

PDA's New Projects to Assist Pharma Manufacturers

PDA has formed a new technical report team and a task force to advance projects to assist pharmaceutical manufacturers in key areas. Both projects were approved by the PDA Science Advisory Board and have spun out of PDA's umbrella Manufacturing Science and Operations Program℠.

"PDA is pleased to sponsor these important projects that will support pharmaceutical manufacturers throughout the industry," said **Richard Johnson,** PDA President & CEO.

This team has been sanctioned to draft industry guidance on the governance and control of big data implementation in manufacturing enterprise to ensure maximization of data insights.

The task force will examine predictive maintenance of equipment using advanced statistical and mathematical methodology. This task force could produce a written case study in the form of a PDA technical report, journal article or other publication type.

Mark Your Calendars for PDA Biopharma Week

PDA is excited to announce the launch of the Association's inaugural *Biopharmaceuticals Week* next year, scheduled for May 6–10 in Long Beach, Calif. Topics at this weeklong series of meetings will touch on biosimilars, cell and gene therapies, vaccines, viral contamination and biopharmaceutical manufacturing. PDA has released a call for abstracts from anyone interested in speaking or presenting a poster. For more information about the *2019 PDA Biopharmaceuticals Week*, visit www.pda.org/global-event-calendar/event-detail/2019-pda-biopharmaceuticals-week.

PDA Volunteer Spotlight

Claire Fritz Briglia

- **Technology Specialist**
- ***MilliporeSigma***
- Member Since | **1996**
- Current City | **Erie, Pennsylvania**
- Originally From | **Emmaus, Pennsylvania**

Do not make assumptions and do not be afraid to ask questions

Tell us about your volunteer activities for PDA.
I have been a member of the *PDA Letter* Editorial Committee and its multimedia subcommittee since the beginning of 2017. Previously, I wrote a couple of articles for the Letter and authored chapters in the PDA/DHI *Environmental Monitoring* book series. I am also a backup instructor for PDA's "Aseptic Processing Training Program."

What is it like serving on the *PDA Letter* Editorial Committee?
Some may assume that being on the committee is time-consuming, but I have found it to be a nice break from my typical job responsibilities. I have really enjoyed being a part of this extremely important messaging for our industry.

If I wanted to write an article for the *PDA Letter,* how would I start?
I would first go to the Letter website for information on the types of submissions and the guidelines. When I am choosing a topic, I think about industry challenges or any topic that needs awareness or clarity.

What benefits can suppliers gain by joining PDA?
I train a lot of end users in microbiology applications and I always stress the value of PDA membership. From the publications to the conferences, it is the absolute best way to keep up with what is going on in the industry and follow current regulatory expectations.

As a supplier, we need to develop the best possible products to address the industry's needs. PDA can be a No. 1 resource in this regard.

What new innovations within the industry excite you?
Automation and robotics excite me the most. I just wish we could adopt new technologies faster. At the same time, I do believe the U.S. FDA is making some positive changes to help support innovation.

What was your favorite class in school?
Any math or science class got me out of bed in the morning! I also really enjoyed working in the analytical chemistry lab when I was a senior in college. It was my first step in understanding how I could apply my chemistry skills in a real job.

pda.org/2019Aseptic

PDA Aseptic Processing

Keep up with the latest trends in Aseptic Processing

2019 SCHEDULE

OPTION 1
Week 1: January 28 – February 1
Week 2: February 25 – March 1

OPTION 2
Week 1: March 18-22
Week 2: April 15 -19

FOR MORE INFORMATION, CONTACT:
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Tel: +1 (301) 656-5900 ext. 103
E-mail: mcintire@pda.org

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For more than 70 years, PDA has been recognized worldwide as a leader in aseptic processing. With the advent of new biological therapies, the importance of proper aseptic processing has never been greater. Turn to PDA for the most comprehensive aseptic processing education, taught in PDA's unique cleanroom filling facility.

PDA's two-week Aseptic Processing training course, taught by industry leading experts in their fields with more than 300 years of combined experience, will give you the training and information needed to properly evaluate and improve your aseptic processes to ensure sterile products. This course provides the perfect balance of hands-on laboratory and lecture training, equipping you with tools and practical experience you can apply immediately on the job.

LEARN HOW TO:

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- Correlate basic microbiology concepts and techniques to multiple aspects of aseptic processing
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- And much more!

SPACE IS LIMITED
These courses routinely sell out, so register today to reserve your seat!

pda.org/2019Aseptic

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PDA is an accredited provider of continuing education, offering high-quality, relevant training for both new and experienced professionals working in industry, government (health authority), and academia. Visit PDAtraining.org for a complete list of PDA training courses.

This course is taught in PDA's U.S. manufacturing training facility.

West Coast Chapter Hosts Women in Biopharma Panel

Lori Richter, ValSource

As I looked around the room at the West Coast Chapter's *Women in the Biopharmaceutical Industry* event Aug. 23, I was enlivened by the energy. Women and men had come from all over Northern California to hear the career journeys of six women panelists involved in various facets of the biopharmaceutical industry.

During the cocktail hour, the 150 participants shared stories with one another, met new people, exchanged business cards and, most importantly, enjoyed an evening of camaraderie after a long work week. Old friends reunited and new friendships developed. As I prepared the mic to moderate the session, I already had a great feeling about how the event was going to progress.

As cocktail hour came to an end, the five panelists—**Catherine Kavanagh**, PhD, **Mandy Sharma**, **Stephanie Yonker**, PhD, **Pat Hancock** and **Ziva Abraham**—and I converged at the front of the room, eager to start the session. Each of us offered a broad range of experience. Some had travelled abroad for business or had even lived abroad for periods of time. While some had several roles in leadership, others preferred being individual contributors. There were directors, company founders, consultants and managers. Hobbies consisted of traveling, cooking and raising horses. Some worked in project management, others in quality systems and legal. I was humbled by the expertise and diversity of the panel but, most of all, how the panelists exuded support and passion for the advancement of women in the biopharmaceutical industry.

During the Q&A, questions touched on such topics as: "What have you done during your career that most pushed you out of your comfort zone?" "As a female leader, what has been the most significant barrier in your career?" "What motivates you every day?" The answers were thought-provoking, passionate and from the heart, leaving the audience with key takeaways to use in their own journeys. Overarching takeaways? Take risks. Push yourself. And ignore the negative voice in your head that says you cannot succeed.

All the panelists truly embraced the saying, "get comfortable with being uncomfortable."

Another common thread was that constant learning and growth is fundamental to career satisfaction. All the panelists truly embraced the saying, "get comfortable with being uncomfortable."

These women always aspired to know more and learn from others, and this intent really emerged throughout the evening as they shared their stories.

During the evening, we laughed, we cried, and we reflected on many key discussion points. The panel was extremely engaging and the audience participation overwhelming. Many people took away amazing advice and inspirational quotes from the panelists. Attendee **Carol Herring** demonstrated her enthusiasm for the evening by sharing one of her favorites from the night: "If you take a leap and it does not work out, leap again." This speaks to risks we all face in our careers. Without the risk, there is no reward. Taking a leap in your career may be the most challenging and most fulfilling move you make. It is one you will always learn from and you can always feel proud that you took that chance on the most important person: Yourself.

PDA's West Coast Chapter hosts many great events such as this. If you are interested in participating in any of these events or in volunteering, please contact the chapter at rsvp@wccpda.com.

PDA Who's Who

Ziva Abraham, President, Microrite, Inc.

Pat Hancock, Quality Site Head, Genentech Vacaville site

Carol Herring, Project Manager, Genentech

Catherine Kavanagh, PhD, Director of Quality, Boehringer-Ingelheim Fremont Inc.

Lori Richter, Senior Consultant, Valsource

Mandy Sharma, CMC Project Leader, Boehringer Ingelheim

Stephanie Yonker, PhD, Vice President of Legal, Alector

PDA Forms New Chapter in Pacific Northwest

PDA is excited to announce the launch of our newest chapter, the Pacific Northwest Chapter. This chapter will provide a local forum for pharmaceutical and biopharmaceutical manufacturing professionals located in Washington, Oregon, Idaho, Alaska and British Columbia.

The following experts will serve as the volunteer officers for the PDA Pacific Northwest Chapter:

President: **Lisa Rutter,** Partner Therapeutics

President-Elect: **Brian Hawkins,** PhD, BioLife Solutions Inc.

Secretary: **Irene Braginskaya,** Nohla Therapeutics

Treasurer: **Anethra Wilson,** Partner Therapeutics

Members At Large: **Alireza Abazari,** PhD, BioLife Solutions Inc., and **Julia Hart,** Aptevo Therapeutics

PDA Education Intern Looks Back: One Year Later

Zion Jackson, Bowie State University

Greetings! My name is **Zion Jackson** and I spent the summer of 2017 as an intern with PDA's Training and Research Institute (TRI).

While parts of my internship were spent working on administrative tasks at my desk, I also had the opportunity to work in the training labs—an opportunity I absolutely enjoyed. My supervisor, **David Talmage,** allowed me to broaden my horizons through very precise assignments. Not only did I learn about the workplace, but I gained great life lessons from this experience as well. This internship required a lot of organizational skill, disciplined focus and time management.

In all honesty, I am not the most organized person. The first day of my internship, however, involved extensive organization. My first task took me two weeks to complete. For this task, I organized important papers from different training sessions into their correct folders. Since these papers were very important, I made sure that all of them were filed correctly. Of course, working with a copier proved a hassle, but is that not the case for all technology? Still, I always made sure to double-check my work and worked at a good pace to do the job right and complete it in a timely fashion.

Working in the labs required more disciplined focus and precision. It came with a lot of responsibilities and rules. Not only for the safety of the individuals in the lab, but also for the tests and training activities being conducted. I set up training sessions and prepared the substances needed for a particular class. For any class to succeed, the setup must be up to par. I was nervous, of course, but I accepted the challenge with confidence. My supervisors were really patient with me and very helpful. Not only did they inform me of what my tasks were, but they educated me about the different machines and activities that take place in the lab. I found it quite interesting to come to work and learn something new every day. In the end, I became comfortable with the labs and felt very welcome. It truly made me feel amazing that they trusted me with such important tasks. While I messed up here and there, they still encouraged me to keep going and always do my best.

I would definitely recommend a person my age ask about this internship and get involved. I enjoyed working with the PDA Education staff every day. Even though I was younger than them, they treated me as if I was one of them. I was treated as a mature adult and their mentoring guided me into a different way of thinking. And, ultimately, I learned the importance of organization and time management. I would love to give a special thanks to my supervisors David Talmage, **Stephanie Ko, Kimberly McIntire** and **Stephanie Grinan.** They pushed me to my limits and helped me every step of the way. I appreciate them

so much, and I hope it was as much of a pleasure having me there as it was for me being there with them.

PDA Who's Who

Stephanie Grinan, Education Coordinator, PDA

Zion Jackson, Student, Bowie State University

Stephanie Ko, Senior Manager, Lecture Education, PDA

Kimberly McIntire, Manager, Education, PDA

David Talmage, Senior Director, Education

Post-Approval Changes Workshop

August 27 | Bethesda, Md.

(l-r) Emma Ramnarine and Anders Vinther lead the workshop

Bayer Facility Tour in Berlin

October 18 | Berlin, Germany

The staff of PDA's European headquarters visited the Bayer manufacturing facility located near their office. Below are photos of them gowned and ready to tour!

(l-r) Ilona Frank, Melanie Decker, Teresa Schubach, Antje Petzholdt, Nadjeschda Gomez-Stahl and Iryna Funke

(l-r) Dirk Stelling, Sylvia Becker, Falk Klar, Julie Tchuya, Elke von Laufenberg, Creixell Espilla-Gilart and Kerstin Wilken

SNAPShot

Standards at PDA

Adding to Our Growing Portfolio of Technical and Scientific Work

Christine Alston-Roberts, PDA

PDA was accredited as a standards development organization in March 2017 by the American National Standards Institute (ANSI). ANSI coordinates standards, conformity assessments and related activities in the United States; they are the official U.S. representative to the International Organization for Standardization (ISO). An American National Standard (ANS) is a voluntary consensus standard, where all materially affected and interested stakeholders, including consumers and the general public, have a voice in the ANS process.

Accreditation by ANSI means meeting the due process-based criteria established in the ANSI Essential Requirements document. Key components include:

- Consensus is reached by representatives from materially affected and interested parties
- Proposed standards undergo public reviews where any member of the public can submit their comments
- Comments are responded to in good faith
- A required appeals process is available

Standards can be generally categorized into documentary standards and reference materials. PDA's standards program will focus on documentary standards. As such, the program will build upon the existing rigorous, volunteer expert-driven scientific processes used to develop PDA's technical documents. Forthcoming PDA standards will follow a very similar path as technical reports **(Figure 1).** PDA's Board of Directors will provide strategic oversight of proposed standards, ensuring standards align with strategic objectives **(Figure 2).** At the next level, the PDA's advisory boards that approve all technical documents will also approve standards. A task force, here referred to as a "consensus body," will be developed comprising experts and stakeholders in the field. Outside input will also be considered.

Continued on page 22

Journal *TOC*

November/December Journal Offers Latest Packaging Research

Two research articles in the November/December *PDA Journal of Pharmaceutical Science and Technology* (journal.pda.org) address packaging. One examines the impact of container closure system integrity during frozen transit and the other looks at delamination.

Review

Jan Duchek and Balazs Havasi, "Analysis of Particulate Matter in Liquid Finished Dosage Forms"

Research

Alejandra Nieto, et al., "Evaluation of Container Closure System Integrity for Storage of Frozen Drug Products: Impact of Capping Force and Transportation"

Massimo Guglielmi, et al., "Delamination propensity of glass containers for pharmaceutical use: a round robin activity looking for a predictive test"

Technology/Application

James Agalloco and Edward Tidswell, "The Boil Test - Strategies for Resistance Determination of Microorganisms"

Kathryn Lee, Markus Lankers, and Oliver Valet, "Identification of Particles in Parenteral Drug Raw Materials"

Rizwan Sharnez, et al. , "Multiproduct Resin Reuse for Biopharmaceutical Manufacturing: Methodology and Acceptance Criteria"

Zhiyun Liu, "A Rapid Microbial Screening Method for In-Process Biologics"

PDA Paper

John Shabushnig, et al., "Achieving 'Zero' Defects for Visible Particles in Injectables"

Commentary

John Ayres, "Conducting Clinical Risk Assessments for Visible Particulate Matter in Parenteral Preparations"

Glass Breakage in Pharmaceutical Packaging

Highly Welcome or Utmost Feared?

Carina Bronnbauer, PhD, SCHOTT

Thanks to low extractable/leachable profiles, small diffusion coefficients and high transparency, glass reigns as the undisputed material of choice for parenteral packaging. For a long time, the only major drawback of glass was believed to be its inherent breakage risk. Yet recent concerns about breakage have prompted some parenteral manufacturers to take another look.

In the pharmaceutical packaging industry, discussions about glass breakage can be traced back to two main areas of context: fill/finish line performance and container closure integrity (CCI). With fill/finish line performance, the question is whether broken containers on the line cause less disruption and yield loss than machine components broken from highly break-resistant containers on the line. With CCI, the concern is that immediate and reliable container failure on the fill/finish line could prevent unrecognized crack formation, channeling container-leakage or ingress into the market.

Regarding both of these areas of interest, three questions should be addressed:

1. What is the right level of container strength and how can it be achieved?

2. At which step of the value chain should the strength and the integrity of the container be investigated?

3. What is the appropriate test scenario regarding container strength and integrity to make container performance predictable?

To answer the first question, a short introduction to glass strength is required. In general, the probability of breakage or the mechanical strength of glass, respectively, is dependent on the existence of surface flaws and the magnitude of applied tensile stress rather than on glass composites ***(1).*** Based on theoretical formulas, like the Griffith equation, one can derive two general rules of thumb: **1)** the bigger the surface flaws, the less tensile stress can be applied until glass breakage occurs, and **2)** glass products with only very small defects can withstand much larger tensile stress before fracturing occurs. Moreover, since no container is fully alike with respect to surface quality, glass breakage can never be exactly predicted.

Based on the tremendous negative impact of surface flaws on mechanical stability of the final product, two approaches are commonly used to control the mechanical strength of glass: (i) minimizing the generation of surface flaws along the full value chain, e.g., via fill/finish line optimization or special glass coatings at the outside of the container, and (ii) lowering the destructive impact of existing surface flaws via post-processing, e.g., via chemical toughening. Within process (ii), intended built-in stress profiles are generated through systematic ion exchange.

The good news is that there is no need for a special glass type for either approach. All common silicate glasses, such as soda-lime, aluminosilicate and borosilicate glass, are suitable. For approach (i) there is no restriction. The bad news is that manipulations of the mechanical strength via chemical toughening not only affect breakage resistance, but may also influence fracturing behavior, glass chemistry of the inner surface and, the extractable/leachable profile of the pharmaceutical container ***(2).*** The last aspect has to be taken into account when it comes to regulatory container approvals and drug shelf life-studies, particularly for drugs already on the market, leading to significant costs due to repetition of shelf-life studies along with other regulatory requirements. Since chemical toughening requires additional post-processing steps, increased purchasing costs for the container itself and additional manufacturing costs must be considered, too. For variations in fracturing behavior, it is the crack formation risk, or CCI and fill/finish line performance that needs to be reinvestigated.

To Chemically Strengthen or Not

To demonstrate possible ambiguous fracturing behaviors, a study compared chemically strengthened and non-strengthened containers. Both types were either clamped between two metal plates while the mechanical load was continuously increased along the vertical axis until breakage occurred, or sawn with a diamond plate to depict the container's fracturing behavior upon crack formation. A chemically strengthened container can withstand high mechanical load if clamped between two metal plates and bursts apart into predominantly superfine particles upon breakage. Conversely, if the same type of container is scratched by a sharp, very stiff material, it suddenly breaks apart into rather large cullets. In contrast, nonstrengthened glass containers withstand less mechanical load if clamped between two metal plates, resulting in much larger fragment sizes compared to a strengthened container. When in contact with a sharp, very stiff material, cracks do not necessarily lead to breakage. Here, even deep furrows can be easily sawn into such containers without full destruction.

The differences in fracturing characteristics between both types of containers can cause different scenarios during container use, such as on filling machines. The first assumption, that strengthened containers allow a higher production yield due to less glass breakage proved incorrect. Since strengthened glass can show even higher mechanical strength than certain machine parts, not only the breakage of glass needs to be considered, but also the destruction of machine components due to too-strongly clamped containers. Thus, an increase of Total Cost of Ownership (TCO) might result, due to longer machine downtimes and a reduction in machine throughput. Taking this into account, an outer coating of nonstrengthened containers that minimizes glass-to-glass contact might work better if aiming for a good production yield.

In theory, but still without statistical evidence, strengthened containers might lower the risk of jeopardizing patients' health through imperceptible ingress of impurities into the aseptic drug, since crack formation on strengthened containers results in immediate breakage.

Accordingly, concerns about the correct container strength cannot be sufficiently addressed as it is rather a question of defining the perfect match between container properties and optimum processing. Here, the supply chain must be factored in as well. How small the risk of a crack or breakage actually is can be exemplified by looking at some statistics; projections estimate 20 billion vials for filling injectable drugs are processed on an annual basis, while only six recalls related to "cracks" and "breakage" were announced within the last six years for borosilicate glass containers ***(3).*** Already starting from a very low-risk potential, the primary goal is to lower it even further in order to finally achieve "zero defects." Thus, what happens if crack formation becomes fully negligible in the future through line optimization? Plus, what if cracks remain undetected?

Three-Step Process for Analysis

This brings us directly to the next question: "At which step of the value chain should the strength and the crack formation risk of the container be investigated?" In general, if the glass surface is not regenerated via additional processing steps, like fire polishing or etching with harsh chemicals, products made of glass will have a nonerasable memory regarding surface defects. In other words, surface flaws on the container accumulate throughout the entire process chain and continuously lead to a reduction of container strength. Considering the entire value chain, from glass melt all the way to the end user, it is obvious that there cannot be one single test scenario for glass breakage or crack formation risk, respectively, that models all the numerous processing steps.

Similar to the recommendation within USP <1207> *Sterile Product Packaging—Integrity Evaluation,* three test stations along the full value chain seem to be reasonable: (Station a) right before, (Station b) during and (Station c) after containers pass through the fill/finish line **(Figure 1).** Of course, if shelf-life stability tests are included, additional studies have to be conducted, too. Conversely, investigations that are supposed to characterize the mechanical stability of glass tubing or freshly converted vials (no coatings, no chemically strengthening, etc.) are rather less informative. For both product categories, there is still a long way to go before the product reaches the end user. Here, it is much more important to focus on the intactness of the glass by detecting any existing surface flaws.

Tests immediately before containers enter the fill/finish line (Station a) are relevant not only for sorting predamaged containers but also for differentiating container categories, like strengthened containers, nonstrengthened containers, bulk containers and ready-to-use containers. Next, in-line monitoring of containers passing through the fill and finish line (Station b) can help identify high-risk areas causing surface flaws on the container. Investigating vials directly after the fill and finish line with respect to mechanical stability and

Figure 1 Along the value chain of pharmaceutical containers. (a), (b) and (c) indicate potential testing stations (*the respective test setups at each station are listed in Table 1*)

Table 1 Possible test methods to investigate either the mechanical strength or the CCI of a container. *destructive test, **nondestructive test

	(a) Before Fill/Finish		(b) During Fill/Finish	(c) After Fill/Finish	
	Test	Resembles	Test	Test	Resembles
	Vertical compression*	e.g., crimping	Visual inspection units**	Headspace analysis**	Ingress through crack/CCI
	Side compression*	e.g., back pressure/clamping during on-ine transportation	Smart skin drone systems**	Vacuum decay**	Ingress through crack/CCI
	Pendulum*	e.g., punctual pressure through metal edges		High voltage**	Ingress through crack/CCI
	Burst pressure*	e.g., Internal pressure variations during lyophilization		Repeat all tests listed in column (a)*	Impact of fill/finish line on final container strength

leakage due to crack formation (Station c) are the most relevant for patient safety since this reflects end-user container stability the most. Since each test station answers a different question of container strength and CCI, each station must be equipped with a different experimental setup.

Table 1 summarizes potential experimental methods that can be applied at the three given stations. Moreover, it clarifies whether the measurement is destructive or nondestructive. Taking into account that container strength tests only allow statistical statements due to the destructive nature of such tests, there can never be a 100% guarantee in terms of container strength. In contrast, tests intending to detect cracks can be both destructive and nondestructive. Cracks are either detectable directly via camera inspection units or indirectly via CCI analysis methods.

As previously mentioned, tests in Station a mainly focus on the investigation of mechanical strength to reflect progress in product development of new container systems. Since mechanical strength cannot be directly implemented into the filling line due to its destructive nature, lab tests need to be developed that try to resemble the numerous mechanical loads to which a container is exposed on a fill/finish line. Possible test scenarios could be vertical compression (e.g., resembling the crimping process), side compression (e.g., resembling back pressure during container transport in depyrogenation tunnel), pendulum (e.g., resembling punctual impact through metal edges) and burst pressure (e.g., resembling pressure differences within a closed container during lyophilization). All respective test scenarios are depicted in **Table 1.** After completing the various mechanical tests, one should not stop with the investigations. Here, subsequent fractographic analysis provides a promising tool to identify the origin of the breakage and possibly ascertain the weakness of the analyzed container ***(4).***

Conducting not just one mechanical stability experiment, but several different tests is very important. The latest in-house studies indicate that each type of container (other glass type, other surface treatment, other converter, etc.) has its own fingerprint when it comes to the correlation between the different mechanical strength tests. For instance, by conducting burst pressure stability tests, the outcome for axial compression is not predictable.

Nowadays, visual camera inspection systems are well established on fill/finish lines for Station b and can even be considered as a standard feature. New technologies, however, have evolved explosively over the last few years. For example, mathematical algorithms based on neural network programming might soon facilitate fast learning and adaptive online inspection units for even small lot sizes with fast-changing container dimensions.

On top of this, another new technology has launched recently. With this, a drone container passes through the complete fill/finish line together with regular glass containers, detecting pressure, spin, tilting and shock. With this approach, optimizing production lines with respect to any potential mechani-

Continued at bottom of page 39

Standards at PDA continued from page 18

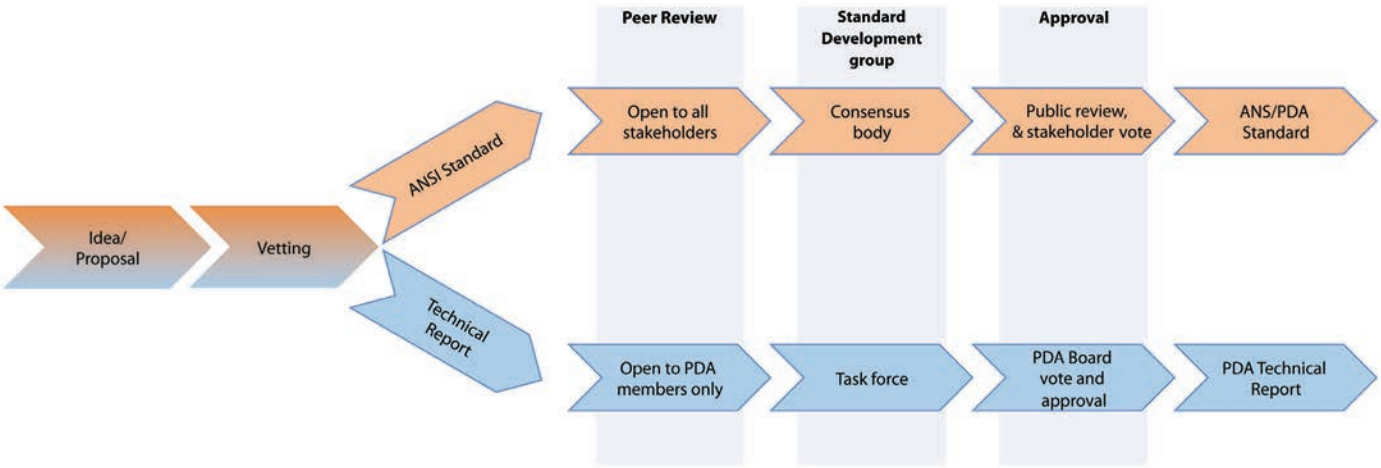

Figure 1 Development of a Standard versus a Technical Report

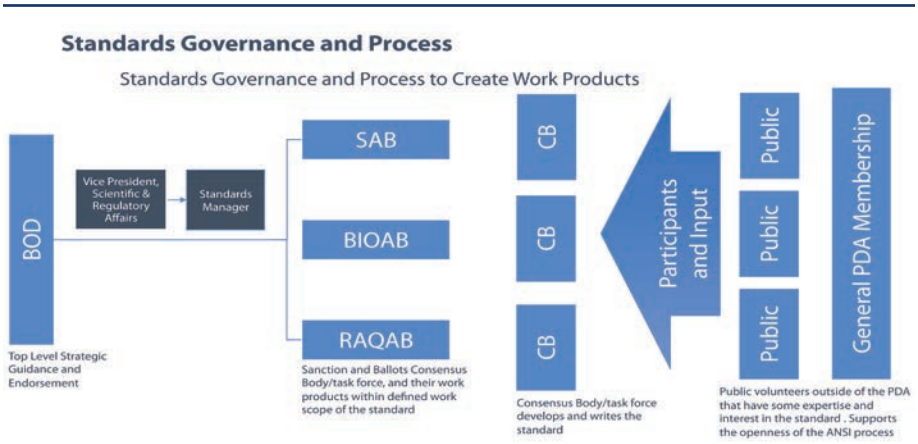

Figure 2 Standards Governance

Existing PDA materials will be used to develop standards along with new information. For example, a standard could be developed as the result of a technical report revision, either replacing the technical report or serving as a companion to the document. While individuals both within and outside the PDA membership can propose a new standard, the vetting process will carefully consider how a proposed standard fits within PDA's mission, such as how the standard would or could be used in a conformity assessment or compliance context. Once endorsed by an Advisory Board, a standards proposal will be sent to ANSI to be checked against other proposed and existing standards, and an open public comment announcement is made for 30 days. This is actually an open call for volunteers to form the consensus body. That group will draft the standard.

Figure 3 shows the general development process for a PDA standard: An expert task force is formed, a draft document is created, the working draft is then delivered to reviewers and the final draft is presented to the Advisory Board and Board of Directors for balloting. Once approved by the Board of Directors, the standard is then finalized for publication and presented to the ANSI executive standard council for review and approval to become an ANS. A 60-day open call for volunteers to serve on the consensus body is made following a new standard announcement.

An important additional step in the standards development process is an open public comment period, in accordance with ANSI rules. Once comments are received, they are deliberated for resolution before the standard is put forward for a consensus vote.

Two Standards Already in Pipeline

PDA's new standards program is already off the ground and running with two projects that have successfully completed the ANSI proposal stage and final team formation is in process. Both proposals are for new standards and address key industry concerns:

BSR/PDA Standard 01-201x, Enhanced Purchasing Controls to Support the Bio-Pharmaceutical, Pharmaceutical, Medical Devices and Combination Products Industries: The proposed standard is intended to address the challenges faced when purchasing, procuring or referencing where specific materials or ingredients came from. This proposal also provides steps to make the responsible party more effective in preventing substandard or adulterated materials from entering the market and potentially harming patients.

BSR/PDA Standard 02-201x, Cryopreservation of Cells for Use in Cell Therapies and Regenerative Medicine Manufacturing: The proposed standard is intended to address the challenges associated with

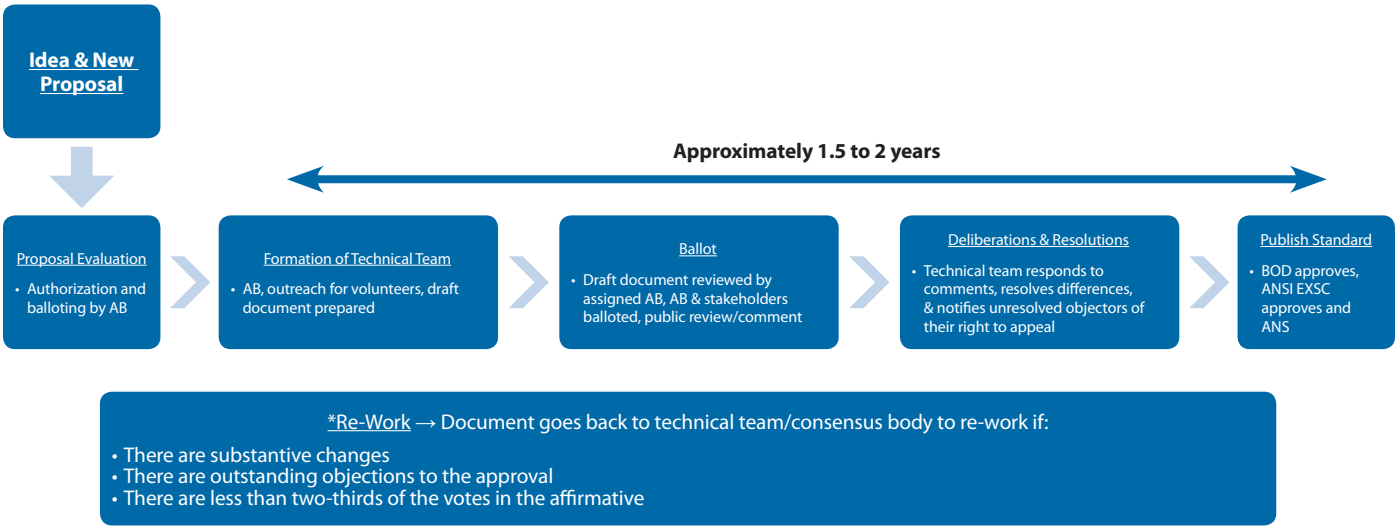

Figure 3 Approximate Standard Development Steps and Time Line

maintaining viable recovery and functionality of cellular therapies and tissue products, discuss the benefits and considerations of low-temperature biopreservation, outline biopreservation best practices for users and propose considerations for incorporating biopreservation best practices into GMP for cell therapy products.

Look for updates on our website as these standards are developed and posted for public comment. You can learn more and get involved by contacting standards@pda.org.

Reconstitution and Storage Times for Lyo Products

A Review of Relevant Literature on Reconstitution and Storage Conditions

Tony Cundell, PhD, Microbiological Consulting, LLC

Lack of regulatory guidance around the reconstitution and storage conditions for lyophilized products, coupled with unofficial yet stringent recommendations for storage times based on laboratory studies, has resulted in inconsistent product labeling. In the process, it also may have increased product contamination, particularly in hospital settings.

Pharmaceutical manufacturers are required to include product preparation instructions including reconstitution, mixing and storage instructions with expiration statements in their product inserts. The regulatory expectations are that the storage conditions, i.e., ambient temperature, refrigeration or frozen and storage times, must be supported by physical, chemical and microbiological stability data generated by the pharmaceutical company. Unfortunately, the details for conducting microbiological stability studies are not contained in cGMP regulations or U.S. FDA guidance documents, but in podium presentations and articles in trade publications by FDA microbiologists ***(1).***

FDA recommends 100 colony-forming units of selected laboratory cultures inoculated into the reconstituted product, with growth defined as a greater than 0.5 log increase in numbers. This recommendation has often resulted in default ambient temperature storage times of six hours or less, depending on the results of microbiological stability studies.

These restrictions may result in the reconstitution of lyophilized products and transfer to IV bags conducted in clinical settings instead of a hospital pharmacy, increasing the risk of microbial contamination. Other issues include discarding satisfactory product stored beyond the recommended storage time, and clinicians actually disregarding instructions for use. The literature clearly indicates that reconstituting drug products at the patient's bedside increases the risk of microbial infection more than seven-fold ***(2),*** while discarding product increases patient care cost and decreases availability of therapeutically valuable product. Clinicians disregarding what they perceive as overly restrictive instructions for use, choosing to follow what they believe to be an acceptable work-around, presents an unfortunate trend and should be actively discouraged.

The FDA position is well known ***(1).*** More recently, however, there has been greater awareness of the use of meta-analysis of microbial contamination studies of parenteral doses prepared under aseptic conditions ***(2,3).*** Although meta-analysis is a powerful tool, it does result in the inclusion of data from flawed studies where best injection practices were not employed, leading to higher reported contamination rates. As summarized in **Table 1,** the mean 0.5% contamination rate of drugs prepared in a pharmacy setting is five-fold higher than the clinical standard of 0.1%, i.e., one in one-thousand dosages contaminated ***(2).*** The data clearly supported preparation in hospital pharmacy and not clinical settings.

Pertinent guidance documents include:

- 21 CFR 211.166 - Current Good Manufacturing Practice for Finished Pharmaceuticals
- ICH Q1A (R2): *Stability Testing of New Drug Substances and Products*
- ICH Q8: *Pharmaceutical Development*
- ICH Q9: *Quality Risk Management*
- *WHO Guidelines for Stability Testing of Pharmaceutical Products Containing Well Established Drug Substances in Conventional Dosage Forms*, WHO Technical Report Series, No. 863, 1996, Annex 5.

[Author Note: None of these documents explicitly discusses reconstitution and storage studies**.]**

Microbial Growth Conditions

Some generalization can be made around microbial growth conditions. With the exemption of the human pathogen *C. albicans* that grows best at 37 °C, fungal growth favors 20-25 °C while bacterial growth favors 30-35 °C storage conditions. All microbial proliferation is inhibited by 2 °C–8 °C and 40 °C storage conditions that are suboptimal for microbial growth. No growth occurs at freezer temperature. Water activities > 0.9 favor the growth of bacteria while Aw <0.9 to > 0.7 favors the growth of yeast and mold. No growth occurs below 0.6. pH while pH < 4.5 will inhibit the growth of yeast and mold. Large molecule products, i.e., biologics are more favorable to microbial growth than small molecule products such as antibiotics, anti-tumor drugs with proteinous nature and lyophilized products with carbohydrates as bulking and stabilizing agents **(Table 2).**

What are the specific microbial contamination risks of hospital-use injectable products? The risk factors are as follows ***(3):***

- Aseptic handling (disinfection of container closure system, level of personnel protective equipment employed and single or multiple manipulations)

Table 1 Meta-Analysis of the Risk of Microbial Contamination of Parenteral Doses Prepared in Hospital Settings

Authors	Number of Studies	Number of Doses	Frequency of Contamination (Prepared in Pharmacy Setting)	Frequency of Contamination (Prepared in Clinical Setting)
Austin et al., 2015	34	16,552	0.5%, 95% CI 0.1 to 1.6%; N = 6.280	3.7%, 95% CI 2.2 to 6.2%; N = 10,272

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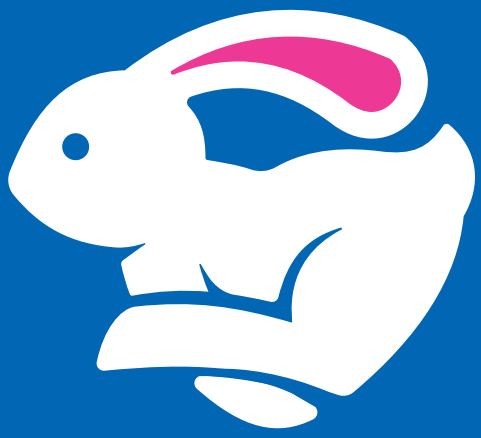

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- Injection site and volume administered (subcutaneous, intramuscular, intravenous and intrathecal administration will have increasing levels of risk by volume and route of administration)
- Usage (single versus multiuse dosage forms)
- Working environment (hospital pharmacy versus clinical setting for reconstitution and transfer to IV bag)
- Operator education and training (pharmacist versus nursing staff)
- Lack of compliance with safe injection practices (reuse of syringes and single-dose vials)
- Storage (storage temperature and duration)

Intrinsic versus Extrinsic

Due to the intrinsic nature of physical and chemical changes, these changes can be classified as stability-indicating. Microbiological stability itself is extrinsic and only occurs if the product is contaminated during preparations prior to administration. **[Note:** Sterile preparations are microbiologically stable**.]**

Comparing challenge organism selections with clinical experience is important ***(2,3).*** Pharmacy isolates used in previous studies have been *S. epidermidis, Bacillus* spp. and *Propionibacterium* spp., while *S. aureus, S. marcescens, Klebsiella* spp., *Enterobacter* spp. and *Candida* spp ***(2,3)*** sufficed as clinical isolates, reinforcing that *E. coli* is a poor choice of a challenge organism as it is not implicated in product contamination and it has a very short generation time that unnecessarily biases determination of reconstitution hold times.

As there is no standardized study protocol, results will vary among different laboratories, resulting in different labeling requirements for similar products **(Table 3).** The study results may be influenced by the following factors:

- Challenge organism selection (quality control organisms, clinical organisms or product contaminants
- Inoculum preparation (commercially prepared, frozen or fresh cultures, growth in liquid or on solid media, washing or dilution of inocula and relative homogeneity of the inocula)
- Inoculum size (choices include <100 cfu, 100 cfu (50 to 200 cfu), or 100–1000 cfu)
- Incubation temperature (2 °C–8 °C, 25 °C or 30 °C
- Incubation time (0, 1, 3, 6, 8, 12, 18 or 24 hours)
- Acceptance criterion (no greater than 1 or 0.5 log increase)
- Terminal incubation time (2–3 times proposed hold time or at least 2 times interval beyond first-count increase) **[Author Note:** Bacteria found in hospital settings will be stressed and will have considerably longer lag times than laboratory cultures and will take longer to grow in reconstituted and stored product**.]**

So what is the appropriate recommended reconstitution and storage time that should be included in product instruction. A risk assessment model found in current USP <797> *Pharmaceutical Compounding – Sterile Preparations* designates the reconstitution, storage and administration for products listed in **Table 3** as having a low-risk level. The instructions for use of approved monoclonal antibodies is highly restrictive and inconsistent, although they share common formulations. The recently published in-process revision to <797> recommends beyond-use dating of Category 1 and 2 compounded sterile preparations held at controlled room temperature of 12 hours and four days respectively. This is inconsistent with the FDA recommendations. A suitable constitution and storage time would be eight hours at room temperature and 24 hours at refrigeration temperature.

Table 2 Carbohydrate Utilization Pattern of Common Injectable Drug Product Contaminants (After Bergey's Manual of Determinative Bacteriology, 9th Edition, 2000)

Microorganisms	Description	Sucrose	Mannitol	Trehalose
E. coli	Gram-negative, rod-shaped fermentative bacterium	±	+	+
S. epidermidis	Gram-positive, facultative anaerobic, coccus	+	-	-
Bacillus spp. (*B. subtilis*)	Gram-positive, spore-forming rods	+	+	+
Propionibacterium spp (*P. acnes*)	Gram-positive, facultative anaerobic, micro-aerophilic, pleomorphoric rods	-	-	-
S. aureus	Gram-positive, facultative anaerobic, coccus	+	+	+
S. merscens; Klebsiella spp.; *Enterobacter* spp	Gram-negative, rod-shaped, facultative anaerobic bacteria	+	+	+
Candida spp (*C. albicans*)	Facultative anaerobic, budding yeast	+	+	+

Conclusions

The dissemination of FDA regulatory requirements via trade publications and podium presentations without publishing a Guidance for Industry with stakeholder review and standard protocols has naturally led to inconsistent implementation. The laboratory model recommended for setting reconstitution and storage conditions with exclusive emphasis on time as a risk factor has resulted in too stringent storage requirements, with the unintended consequence of increasing product contamination.

References

1. Metcalfe, J. W., "Microbiological Quality of Drug Products after Penetration of the Container System for Dose Preparation Prior to Patient Administration." *American Pharmaceutical Review.* (Feb. 1, 2009)

Table 3 Names, Formulation and Reconstitution and Storage Instructions of Representative Monoclonal Antibodies Marketed in the U.S. from Package Inserts

Monoclonal Antibody	Formulation	Reconstitution and Storage Instructions
LLARIS (canakinumab) 150 mg/mL Novartis	Sucrose, 92.4mg/mL; L-histidine; polysorbate 80	Used within 60 minutes of reconstitution. Otherwise, it should be refrigerated at 2 °C–8 °C and used within 4 hours of reconstitution
XOLAIR (omalizumab) 125 mg/mL Genentech	Sucrose, 90 mg/mL; L-histidine; polysorbate 80	Use within 8 hours following reconstitution when stored in the vial at 2 °C–8 °C or within 4 hours of reconstitution when stored at room temperature.
RAPTIVA (efalizumab) 100 mg/mL Genentech	Sucrose, 82 mg/mL; L-histidine; polysorbate 80	If the reconstituted product is not used immediately, store at room temperature and use within 8 hours
HERCAPTIN (tratuzumab) 21 mg/mL Genentech	Trehalose dehydrate, 20 mg/mL; L-histidine; polysorbate 80	Reconstitution with SWFI, as it contains no preservative and is intended for single-dose only. If not used immediately, store the reconstituted solution for up to 24 hours at 2 °C–8 °C; discard any unused product after 24 hours.
REMICADE (infliximab) 10 mg/mL J & J	Sucrose, 500 mg; polysorbate 80, monobasic sodium phosphate, monohydrate, and dibasic sodium phosphate, dihydrate	Infusion should begin within 3 hours of reconstitution and dilution. The infusion must be administered over a period of not less than 2 hours.
SIMULECT (basiliximab) 4 mg/mL Novartis	Each 20 mg vial contains 20 mg basiliximab, 7.21 mg monobasic potassium phosphate, 0.99 mg disodium hydrogen phosphate (anhydrous), 1.61 mg sodium chloride, 20 mg sucrose, 80 mg mannitol and 40 mg glycine	Reconstituted in 5 mL of Sterile Water for Injection, USP. Product may be stored at 2 °C–8 °C for 24 hours or at room temperature for 4 hours.
KEYTRUDA 25 mg/mL Merck & Co.	L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg)	At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the infusion solution in the IV bag and the duration of infusion. Under refrigeration at 2 °C–8 °C for no more than 24 hours from the time of reconstitution.

2. Austin, P.D., Hand, K.S., and Elia, M., "Systematic review and meta-analysis of the risk of microbial contamination of parenteral doses prepared under aseptic techniques in clinical and pharmaceutical environments: an update." *The Journal of Hospital Infection* 91(2015): 1–33.
3. Suvikas-Peltonen, E., et al., "Incorrect aseptic techniques in medicine preparation and recommendations for safer practices: a systematic review." *European Journal of Hospital Pharmacy* 24 (2017): 175–181

About the Author

Tony Cundell, PhD, consults with a number of pharmaceutical, consumer health and dietary supplement companies, microbiology instrument manufacturers, contract testing laboratories and sterile compounding pharmacies in the areas of microbial risk assessment, regulatory affairs, and microbiological testing.

FDA's ORA Realignment, MRA, NIPP, Concept of Operations:

How it All Fits Together

Rebecca Stauffer, PDA

> Over the past 25 years, globalization of manufacturing has prompted FDA to change its regulatory landscape

Just over a year ago, the U.S. FDA released detailed information about the restructuring of the newly realigned Office of Regulatory Affairs (ORA) ***(1).*** **Alonza Cruse,** Director, Office of Pharmaceutical Quality Operations, ORA, provided an update on this and other ORA initiatives on Sept. 24 in the second plenary of the *2018 PDA/FDA Joint Regulatory Conference.*

This realignment, coupled with the recent Mutual Reliance Agreement (MRA), is enabling ORA to refocus many of its efforts and reallocate resources, which is expected to impact the pharma industry.

The realignment of ORA inspections from a regional to a commodity focus has been welcomed by industry ***(2).*** Previously, FDA inspectors were region-based, inspecting different types of facilities. For example, an inspector might visit a parenteral manufacturing site one week and a food facility the next. Consequently, some inspectors may have lacked specific knowledge about the nature of the plants they were inspecting. With the commodity focus, pharma inspectors only inspect pharmaceutical sites.

"We feel that level of expertise will certainly help not only provide a better work product, but will help [us] better understand the industry we are working in," Cruse stated in his opening remarks.

Article at a Glance

- FDA Office of Regulatory Affairs has moved to a commodity-based approach
- MRA expected to help with workload
- New initiative targets never-inspected companies

His group is currently divided into four field divisions:

- **Division 1** (HQ in New Jersey)
- **Division 2** (HQ in Dallas)
- **Division 3** (HQ in Detroit)
- **Division 4** (HQ in Los Angeles)

Cruz also oversees two other divisions, one responsible for foreign inspections and one on special programs. In light of recent alarming events, FDA inspections of foreign facilities has heightened.

"Over the past 25 years, globalization of manufacturing has prompted FDA to change its regulatory landscape," Cruse said, noting that it "adds to the complexities of the supply chain [industry] works with every day."

Although the Agency has been challenged to keep pace with the emerging focus on globalization, it has established frameworks for ensuring that all drug products meet the same quality standards. An integral part of this involves inspections of foreign manufacturing sites.

"We need to make sure our inspections are prioritized based on potential risk to the patient and that we are using our resources efficiently," he said. Cruse then delved into the Agency's site selection model and the factors that determine when a site should be inspected. Among other factors, this includes compliance history, recall trends, time since last inspection, inherent risk to the drug or drug product being manufactured and process complexity.

Overseas facilities may also be inspected by staff in the Agency's foreign offices in China, India and Latin America.

MRA to Enable ORA Flexibility

"In addition to maximizing our resources and efficiency, we also pursued other opportunities to collaborate with other countries," Cruse said, referring to the MRA between the United States and the European Union. The MRA allows U.S. and EU regulators to use each other's GMP inspections of pharmaceutical manufacturing facilities ***(3).***

With the MRA, Cruse explained that FDA "can recognize drug inspections conducted by foreign regulatory authorities that meet U.S. requirements. In doing so, we can dedicate investigators' time to those sites that pose a greater risk."

This risk-based approach to inspections is sorely needed due to the large numbers of manufacturing sites around the world. According to Cruse, as of fiscal year 2017, 5,063 sites manufacturing drugs for humans are subject to FDA surveillance inspections, and a little more than 3,000 of those sites are based outside the United States.

"To accomplish this critical work, we need to maximize our resources around the globe, which is why FDA uses its risk-based site selection model to ensure that inspection resources are allocated in the most efficient and appropriate manner," he explained. This risk-based site inspection model instructs inspectors to focus the majority of their inspection efforts on the sites that represent the greatest risk.

After each inspection, FDA assesses the inspection findings and classifies them into one of three categories: 1) no action needed, 2) voluntary action indicated and 3) official action indicated. This information can be found in the Agency's recently updated inspection classification database, which now includes information from inspection reports from recognized foreign regulators.

"While we make an effort to ensure transparency, it is important to note that the numbers in the database do not account for every inspection FDA conducts at any given time," Cruse emphasized. "These represent a subset of inspections that have received final classification. We classify inspections on a rolling basis, taking a thorough look at all relevant information." ➤

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pda.org/2018NovEMCS

15-16
■ **Single Use Systems for the Manufacturing of Parenteral Products**
Bethesda, MD
pda.org/2018SUS

22
Project Management in the Pharmaceutical Industry – Challenges and Possibilities
Berlin, Germany
pda.rog/EU/PM2018

27-28
Pharmaceutical Freeze Drying Technology
Seville, Spain
pda.org/EU/FreezeDrying2018

27-28
11th Workshop on Monoclonal Antibodies
Seville, Spain
pda.org/EU/MABS2018

29
Application of a Risk-Based Approach to Freeze-Drying Processes
Seville, Spain
pda.org/EU/RBP2018

29-30
Development of a Freeze-Drying Process
Seville, Spain
pda.org/EU/FDProcess2018

29-30
Extractables & Leachables
Seville, Spain
pda.org/EU/E-and-L2018

29-30
CMC Regulatory Compliance for Biopharmaceuticals
Seville, Spain
pda.org/EU/cmc-regulatory2018

DECEMBER

3-6
SOLD OUT
Fundamentals of Aseptic Processing – Option 5
Bethesda, MD
pda.org/2018DECFundAP

7
NEW COURSE
Assay Validation by Design
Bethesda, MD
pda.org/2018Assay

11
PRESENTED IN GERMAN
Annex 1 Workshop
Berlin, Germany
pda.org/EU/Annex1_Berlin

11-13
■ **Recommended Practices in Manual Aseptic Processes**
Bethesda, MD
pda.org/2018RPAP

13
NEW COURSE
Passive Thermal Protection Systems for Global Distribution: Qualification and Operational Guidance
Bethesda, MD
pda.org/2018Thermal

JANUARY

28-1
2019 PDA Aseptic Processing – Option 1
Week 2: Feb 25-Mar. 1
Bethesda, MD
pda.org/2019Aseptic1

FEBRUARY

26-28
Understanding Sterilization Training Course
Albuzzano, Italy
pda.org/EU/sterile2019

Denotes laboratory courses taught in Europe. | ■ This course is taught in PDA's U.S. manufacturing training facility.

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

MARCH

11-13
2019 PDA Annual Meeting
San Diego, CA
pda.org/2019Annual

18-22
2019 PDA Aseptic Processing – Option 2
Week 2: Apr. 15-19
Bethesda, MD
pda.org/2019Aseptic2

18
Pre-Filled Syringes Interest Group Meeting
Venice, Italy
pda.org/EU-IG-PFS19

19-20
Parenteral Packaging
Venice, Italy
pda.org/EU/parpack2019

21
Container Closure Development
Venice, Italy
pda.org/EU/CCD2019

21-22
Extractables & Leachables
Venice, Italy
pda.org/EU/el2019

21
Packaging Science Interest Group Meeting
Venice, Italy
pda.org/EU-IG-PS19

25-29
Freeze Drying in Practice
Osterode am Harz, Germany
pda.org/EU/fdp2019

26-27
Temperature Controlled Distribution
Voorhout, The Netherlands
pda.org/EU/TCD2019

PLAN AHEAD FOR 2019

Registration is now open for PDA's 2019 Signature Events

APRIL

23-24
2019 PDA Visual Inspection Forum
Washington, DC | *pda.org/2019Visual*

MAY

16-17
Pharmacopoeia Conference
European Location Coming Soon | *pda.org/EU/pharma2019*

JUNE

25-26
4th PDA Europe Annual Meeting
Amsterdam, The Netherlands | *pda.org/EU/Annual2019*

OCTOBER

21-23
14th Annual PDA Global Conference on Pharmaceutical Microbiology
Bethesda, MD | *pda.org/2019Micro*

22-23
2019 The Universe of Pre-Filled Syringes and Injection Devices
Gothenburg, Sweden | *pda.org/EU/2019UPS*

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He further stressed that inspections are only one way the Agency determines quality; they should not be considered the final Agency action. FDA further drives support for quality through its guidance documents and testing of drug products.

Inspections Not For Peanuts

Cruse then discussed with the audience an initiative ORA started in 2017 to inspect the entire inventory of drug firms over a three-year span. A review of this inventory showed that there were facilities with no FDA inspection history, which meant ORA had no way to assess a level of risk for these sites, even if they were manufacturing so-called "low risk" products, such as tablets.

While some would argue that inspecting such low-risk sites should not be a priority, despite their no-inspection history, Cruse used the example of a common food product found in many homes with small children: peanut butter. In fact, he shared an amusing anecdote of how his children were always requesting more peanut butter, until the day he went to make a sandwich and found numerous, half-used jars of peanut butter on the shelf in his pantry. As a parent, he never thought twice about buying peanut butter for his children until an extensive recall of peanut products in 2008 due to *Salmonella* contamination.

"Peanut butter. A safe product, as I saw it and how many others probably saw the product," he stressed. "So, I never say something is bogus until we make that determination."

In fact, when looking at the numbers, in FY 2017, those facilities that had never been inspected had a violation rate of 25%. For the facilities the Agency had been routinely inspecting, the violation rate was about 5%. These numbers are to be expected as those never-inspected facilities "would not be used to the routine of the rigor of an inspection conducted by FDA."

A number of advisory actions, namely 38 warning letters, resulted from inspections of these facilities.

"Some of those warning letters focused on refusals, others for a specific cGMP violation," Cruse said. In addition, some import alerts were issued. He attributes much of these findings to ORA's realignment.

> "Between 2011 and 2017, the number of registered drug facilities in China increased by 75% and almost a 65% increase in India"

"One upstart of being a vertically integrated-minded organization is that now we are able to take on broader initiatives and take a really good comprehensive look at the entire pharma inventory."

In addition to freeing up resources for FDA to inspect never-before-inspected sites, the MRA also has allowed the Agency to take a closer look at facilities in other parts of the world besides the United States and European Union as it also allows for inspection findings from other regions to be used, provided they are recognized by each agency. These can be critical if sites are located in areas impacted by geopolitical strife, natural disasters or any other finding for which the U.S. State Department has designated a location as dangerous.

And the number of international inspection sites is growing.

"We conducted a review of FDA inspections and found that between 2011 and 2016, FDA inspected facilities in the EU more than any other region. This certainly made sense at the time…but, as you know, the drug manufacturing landscape has certainly changed.," he explained. Between 2011 and 2017, the number of registered drug facilities in China increased by 75% and with almost a 65% increase in India.

Additionally, he pointed out that the rates of violations were fairly low for EU sites as opposed to sites in other locations.

Adding to the challenge, the European Union only has to conduct one positive capability assessment (an analysis of each country's regulatory/inspectorate body) while FDA has to conduct 28, one for each EU country. So far, FDA has conducted approximately half of the assessments required and these assessments are continuing on a rolling basis. Once FDA has assessed a country, ORA reviews the reports and sets a classification similar to a classification audit resulting from an FDA inspection. All capability assessments are scheduled to be completed by July 2019.

Cruse went on to explain that the FDA and the European Union have already begun exchanging GMP documents. When analyzing a country, CDER reviews the site selection list against those countries where "we have conducted capability assessments and we pull those countries' facilities out of our site selection model."

If these countries have not had a recent inspection, FDA may elect to conduct one.

A Streamlined Strategic Framework

Another change within FDA Cruse related is what the Agency refers to as the "Concept of Operations." According to a document signed last June between the heads of ORA and CDER, this framework is intended to streamline FDA processes for inspection and compliance through clearer roles and better established timelines.

"This 'strategic framework,' as I like to call it, puts us not only in line with user fee agreement activity but actually allows us to increase our transparency," he said. He further explained that the inspection database he referenced earlier is part of this new strategic framework.

The Concept of Operations covers surveillance inspections, pre-approval ➤

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inspections, post-approval inspections and for-cause inspections.

"It outlines workflows and responsibilities," Cruse said. "It really helps to bring a singular focus to the major work product coming out of ORA and CDER...we think it brings to us a level of improved efficiency."

As part of the Concept of Operations approach, drug reviewers and investigators collaborate on applications. This process provides greater accountability for ORA due to regular updates and reviews, particularly regarding inspection write-ups.

Cruse also gave an update on the New Inspection Protocol Project (NIPP). This initiative aims to support enhanced quality within pharmaceutical manufacturing facilities.

"One area of focus within this initiative is continuing to create a report that is not only streamlined but gives us an opportunity to get metrics...as you know, our inspection reports are narrative in nature and it becomes difficult if we are looking to attract and trend issues," he said.

As part of NIPP, ORA plans to roll out the Sterile Aseptic Compliance Program next month. Other upcoming protocols will be grouped in the nonsterile space but no time line has been established yet for when those protocols will be unveiled.

All in all, ORA continues its efforts at restructuring and streamlining inspection operations. Many of these changes are still fairly new, so time will tell when any impact will truly be felt. Yet, one thing is clear: industry can continue to expect further streamlining within ORA.

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About the Expert

Alonza Cruse is Director of the Office of Pharmaceutical Quality Operations (OPQO) within the FDA Office of Regulatory Affairs (ORA). His office is responsible for all pharmaceutical quality inspections and investigations, working in conjunction with CDER and the Center for Veterinary Medicine (CVM).

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Process' Interrupted

The Effect of Gamma Irradiation Process Interruption on Microbial Resistance of *G. stearothermophilus*

Fatima Hasanain, Polymer Materials Specialist, Nordion (Canada) Inc.

Sterilization process monitoring and control is key to product safety in the pharma industry. ISO/AAMI 11137-1 addresses the importance of monitoring radiation process parameters to ensure products have been processed according to specification. Radiation sterilization standards generally state that any doses delivered to product are cumulative, regardless of whether the dose is delivered all at once or whether there is a process interruption, such as correcting an issue with the conveyor system. That is certainly the case with regard to radiation effects on product. Whether or not multiple doses delivered with a process interruption in between doses are likewise cumulative with respect to microbial inactivation requires analysis. Although ISO/AAMI 11137-1 describes the requirement to document process interruption, it does not include references to describe the effect of process interruption on microbial resistance to radiation.

A recent study analyzed the effect of gamma irradiation process interruption on microbial resistance of *G. stearothermophilus* spores. Experiments were conducted at different process interruption times (four hours, one day, one week) without temperature control in both a wet and a dry state. The interruption times were selected to represent typical and worst-case scenarios for when interruptions occur during normal practice. As published D-values can vary significantly, based on many factors, the target doses used for the experiments were determined based on initial D-value studies performed. The D-value study demonstrated that 1.55 kGy would be an appropriate D-value to use for the cumulative dose studies. The target doses were calculated to provide log reductions into the fraction-negative region, where some of the test samples would be positive for growth and some would be negative for growth. Some variation around the calculated target dose was required (i.e., slight variations in D-values used in the calculations) to obtain fraction-negative data. The fraction-negative approach was selected early in the process as the other option for D-value determination, the survivor curve, is a more complex microbiological test. It evaluates the resistance of the microorganisms in the middle of the death curve rather than at the tail end.

> **The data presented also show no microbial growth or cellular repair occurring during the process interruption**

Figure 1 Radiation Resistance of *G. stearothermophilus* at Different Interruption Times

(Where no test samples were positive for growth, no calculation could be performed, thus no bar is provided)

The results of *G. stearothermophilus* spores exposed to gamma irradiation at different process interruptions indicate that *G. stearothermophilus* spores, whether in the spore suspension or inoculated on disks and irradiated either dry or wet, do not vary significantly in their radiation resistance **(Figure 1).** In addition, their resistance did not vary significantly when applying different initial doses of either 5-log or 2-log. Having the data from two different, identical runs helped in understanding the typical variation that occurs from test to test. It might appear that the wet suspension and wet disk results indicate a higher resistance than the dry disks. Although the data seem to support this, the sample size is unlikely to be significant enough to statistically justify that this is the case.

Random positives were obtained at different conditions but were not consistent with the sample condition (wet or dry) or how the dose was delivered to the samples. These anomalies might be due to natural variation in *G. stearothermophilus* titer from sample to sample, variations in spore resistance throughout the population or typical human variation during the handling process. This phenomenon is common when reviewing D-value determination data, especially when the delivered lethality is targeting the fraction-negative range.

The data do seem to support that the dose applied is appropriate and in the fraction-negative range, as demonstrated by obtaining mostly no growth in the tests (37 out of 44 different conditions tested) and obtaining partial growth in seven out of the 44 conditions tested **(Table 1).** In this dataset, if there was a significant difference in the microorganism resistance due to process interruptions, it should have been visible.

The third run, performed with use of a lower D-value to calculate the doses to be applied, did not result in a higher number of positives as expected. This might help to demonstrate the variability that can occur in D-value determination tests of this nature. The D-value indicating the radiation resistance for the *G. stearothermophilus* spores at different interruption rates was calculated at the range of 1.39–1.67 kGy.

Gamma irradiation process interruption in wet and dry conditions did not result in a difference in the radiation resistance of *G. stearothermophilus*. The data presented also show no microbial growth or cellular repair occurring during the process interruption, indicating that the same established sterilization dose can be used despite the process interruption. Although no increase in radiation resistance was observed in water, the presence of other microbial growth factors (such as growth medium instead of water) or other microorganisms (such as vegetative microorganisms or water-borne microorganisms instead of spores) and the impact that might be present during process interruption when applying the required sterilization dose must be considered for future analysis.

[Editor's Note: This article is based on the poster the author presented at the *2017 PDA 12th Annual Global Conference on Pharmaceutical Microbiology*.**]**

About the Author

Fatima Hasanain, is a Polymer Materials Specialist for Nordion (Canada) Inc. - a Sotera Health company. She has varying areas of expertise in radiation effects on polymer materials and gamma sterilization.

Table 1 Radiation Resistance for *G. stearothermophilus* in Wet and Dry Conditions at Different Process Interruption Rates

			Run#1 D-Value 1.55		Run#2 D-Value 1.55		Run#3 D-Value 1.40	
		Type	# Positive Over # Tested	Calculated D-value (kGy)	# Positive Over # Tested	Calculated D-value (kGy)	# Positive Over # Tested	Calculated D-value (kGy)
Controls		Wet suspension	5/10	1.67	0/10		2/10	1.39
		Dry disks	0/10		0/10		0/10	
		Wet disks	0/10		0/10		0/10	
Log 5 then Log 2	4 hrs	Wet suspension	3/10	1.60	0/10			
		Dry disks	0/10		0/10			
		Wet disks	0/10		1/10	1.51		
	1 day	Wet suspension	3/10	1.60	0/10			
		Dry disks	0/10		0/10			
		Wet disks	0/10		0/10			
	1 week	Wet suspension	0/10		0/10			
		Dry disks	0/10		0/10			
		Wet disks	0/10		0/10			
Log 2 then Log 5	4 hrs	Wet suspension	0/10		0/10		0/10	
		Dry disks	0/10		0/10		0/10	
		Wet disks	0/10		0/10		0/10	
	1 day	Wet suspension	N/P		0/10		2/10	1.39
		Dry disks	0/10		1/10	1.51	0/10	
		Wet disks	0/10		4/10	1.66	0/10	
	1 week	Wet suspension	0/10		0/10		0/10	
		Dry disks	0/10		0/10		0/10	
		Wet disks	1/10	1.51	0/10		0/10	

Wet suspension titer: 2.4×10^6
Disk titer: 1.8×10^6
7 log reduction dose: 10.9 kGy (Runs 1 and 2)
5 log reduction dose: 7.8 kGy (Runs 1 and 2)
2 log reduction dose: 3.1 kGy (Runs 1 and 2)
7 log reduction dose: 9.8 kGy (Run 3)
5 log reduction dose: 7.0 kGy (Run 3)
2 log reduction dose: 2.8 kGy (Run 3)
N/P: Not performed at this condition in this run

Glass Breakage in Pharmaceutical Packaging continued from page 21

cal stress that may cause surface flaw generation, and thus CCI issues, is now possible. Once identified, high-risk areas within production are often easy to eliminate. Since smoothly running lines accompany low production losses, this new method may reduce TCO, too ***(5).***

Coming to Station c—the most crucial indicator for ensuring patients' health—nondestructive test methods to ensure API policy for CCI investigations should be indispensable for future pharmaceutical packaging. So far, however, regulators only prescribe "100% integrity testing" for fused containers like glass ampoules ***(6).*** For other types of containers (syringes, vials or cartridges), such tests remain only a recommendation ***(7).*** Nonetheless, on-line, fully integrated CCI inspection units like high-voltage leak-detection modules, vacuum and pressure decay technologies are already available and well established on the market. Machine outputs of up to 600 containers/min are becoming more common. Hence, there is no longer a limitation regarding the technical feasibility of 100% online inspection systems. Despite CCI evaluation, the mechanical strength of the container also has to be examined. By repeating the analysis described for Station a, potential weaknesses in the fill/finish line might be identified. Moreover, only at this stage can the "real" mechanical stability of a used container be evaluated.

To conclude, all types of containers have their own specific advantages or disadvantages regarding crack formation risk and processability. Still, not all the solutions outlined will enable full control over the inherent nature of glass breakage. Yet well-positioned measurement setups in combination with new technology can help to make it more assessable. **[Editor's Note:** The online version of this article includes additional figures/tables**.]**

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About the Author

Carina Bronnbauer, PhD, is responsible for product management for technical and pharmaceutical tubing at Schott.

Hidden Contamination in Starting Materials

Are Your APIs Free of Dirt?

Annette Kirsch, PhD, Merck KGaA

Contamination by foreign particles has been covered only to a small extent in regulatory and compendial guidelines, and, even then, mostly for parenteral products. ***(1–5).*** The European Pharmacopoeia only covers particle contamination of oral herbal medicines. ***(6).*** To cover this gap, the Active Pharmaceutical Ingredients Committee (APIC) and the International Pharmaceutical Excipients Council (IPEC) published position papers in 2015 explaining how pharmaceutical manufacturers should deal with particles in APIs and excipients ***(7,8).*** Additionally, PDA recently stepped in and published *Technical Report No. 78: Particulate Matter in Oral Dosage Forms* in December 2017 to complement the pharmacopeial guidance for oral dosage forms ***(9).***

All these guidelines and position papers deal with visible particles in APIs, excipients or pharmaceutical dosage forms. But there is an additional facet to purity: the level of contamination by small and subvisible particles present in an API or excipient that stems from abbreviated manufacturing processes (i.e., not thoroughly cleaning intermediate steps from byproducts), breakdown of equipment caused by insufficient maintenance of facilities or containers, packaging materials and other external particle sources.

The appearance test—distributing several grams of the product on a suitable background and dispersing it evenly to detect visible particles—is standard cGMP. But the level of invisible overall hidden contamination ("background dirt") is not assessed by this procedure. Particulate matter is not homogenously distributed in a material, so it is difficult to detect and must be prevented.

Figure 1 Filter Showing a Low Level of Metformin Contamination (Manufacturer A)

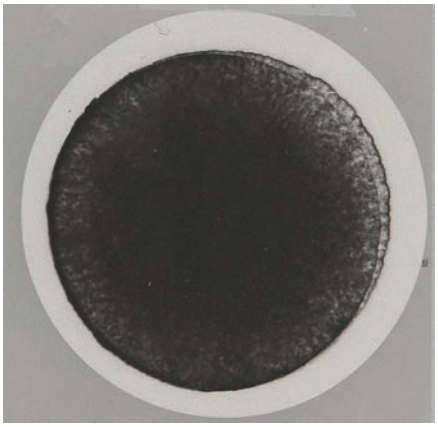


Figure 2 Filter Showing a High Level of Metformin Contamination – Black Particulate Matter (Manufacturer B)

> "the filter test is a good measure to compare the manufacturing process"

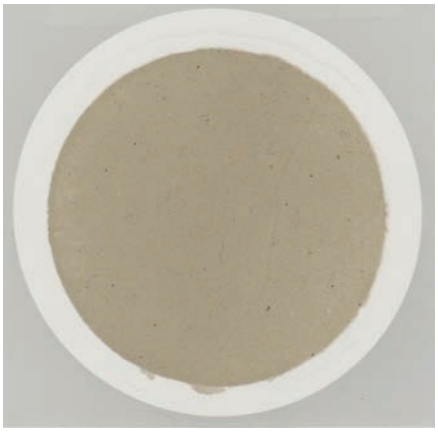


Figure 3 High Level of Metformin Contamination – Brown and Black Particulate Matter (Manufacturer C)

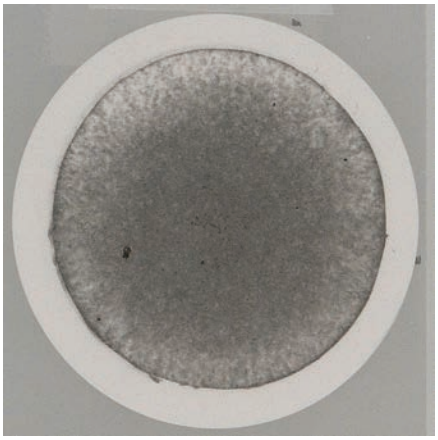


Figure 4 High Level of Metformin Contamination – Black Particulate Matter and Big Brown Particle (Manufacturer D)

Figure 5 Blank Filter Showing the Level of Contamination Caused by the Lab Environment

Checking for Hidden Contamination

A suitable method to check for hidden contamination is the filter test described in the APIC guideline ***(7).*** A representative amount of the material in question is dissolved in a suitable solvent and run through a filter which is then analyzed for particles and color. The coloring, mostly grey, brown or red, can come from a lot of very small particles or from the solution color. Particles of greater than 1 mm should not be present. The solvent and reagents used should not cause any tainting or any other changes to the filter. This simple filter test, including a blank determination to assess contamination from the lab environment, can be done in all quality control laboratories, preferably under a laminar flow hood or in a protected box.

A choice of methods as well as a general process to analyze particulate is offered in TR-78 ***(9).*** One can look for hidden contamination based on the example below, which draws from the technical report. This test assesses the purity of metformin hydrochloride.

In a 5L beaker, 640 g metformin hydrochloride in 3200 mL ultrapure water is stirred until completely dissolved. The solution is then filtered over a nitrocellulose filter (porosity 12 µm, diameter 47 mm) using a vacuum filtration unit. As a blank value, 3200 mL ultrapure water is filtered over another filter.

The test should be done under a laminar flow hood to prevent foreign material present in the lab air from contaminating the solution or filter. All equipment must be rinsed thoroughly with ultrapure water directly before use.

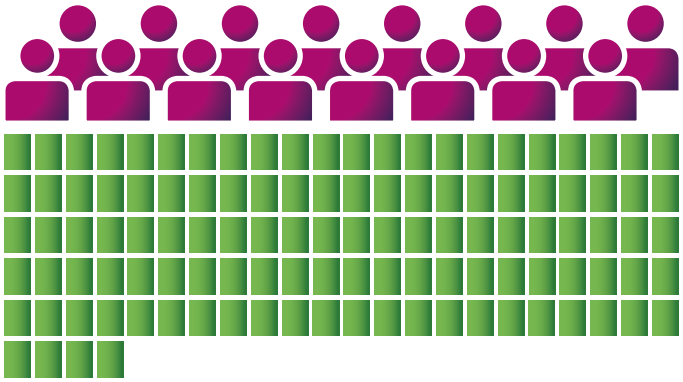
The assessment of the filter is done with the eye and using a magnifying glass with an LED light. The particle size can be measured using a magnifying glass with graduation or using a microscope. Particles

Continued at bottom of page 44

Annex 1
Are You Prepared?

The publicaion of the draft revision of **Annex 1 last December** has lead to considerable discussion within the industry. The final revision may be issued before the end of 2018.

The final Annex 1 revision will be adopted by the European Union (28 member states), PIC/S (54 agencies), WHO (194 agencies) and more!



These 16 experts represented **14 countries** from Europe, Japan and the United States.

A **16**-member PDA commenting team led by **Hal Baseman** and **Gabriele Gori** submitted **114** comments in March.

The European Commission received more than **6200 comments**

Hot Button Topics in the Revision Include

- Introduction of Quality Risk Management
- Contamination Control Strategy
- Pre-Use Post-Sterilization Integrity Testing (PUPSIT)
- 5.0 µm Particles
- Requalification of Facilities
- Media Fills

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SNAPShot

PDA, IPEC Task Force to Develop Joint Excipients TR

Eva Urban, Celgene International Sarl, and Frithjof Holtz, Merck KGaA

Excipients serve a critical role in the production of final dosage forms for drug products and biologics as they help the product fulfill its purpose ***(1).*** Recognizing this critical role, recent EU regulations require manufacturers to ensure appropriate levels of GMP for excipients through application of formalized risk assessments ***(2,3).*** As of March 21, 2016, excipient users/drug manufacturers in the European Union are legally mandated to perform needed assessments of excipient use/function throughout the entire supply chain.

A task force comprising representatives from both PDA and the International Pharmaceutical Excipients Council (IPEC) recently held a face-to-face meeting in Berlin to discuss developing a PDA technical report on the topic. Some U.S. colleagues even took time out of their evenings to phone in via Web conferencing.

In this meeting, representatives from pharma companies presented models for global solutions to introduce risk assessments for all excipients (oral, parenteral, inhalation, etc.). These examples will serve as generic risk assessment models within the planned technical report. The meeting also covered other hot topics, such as lifecycle management, complicated supply chains and benefits of the risk assessment. A supply chain matrix will be included within the technical report that outlines the different responsibilities of all parties within the supply chain, including brokers and contract manufacturing organizations.

The task force has completed a draft of the technical report's overall framework. Now, the group has split into subgroups to work on detailed sections and key topics, such as risk mitigation. Currently, the task force hopes to have the technical report published sometime in Q1 of 2019.

Both PDA and the IPEC Federation believe that it is crucial to present "one voice" concerning the legal, regulatory and related issues around excipients, so this joint initiative will deliver one technical document that addresses the complex challenges of implementing risk assessments in this context. The IPEC Federation sees a great benefit in this collaboration, bringing in IPEC's excipient expertise from one side and the drug product manufacturer's perspective through PDA.

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Hidden Contamination in Starting Materials continued from page 41

that also show up on the blank filter come from the laboratory environment and are not counted.

Figures 1–5 show several examples of the metformin filter test, all of which meet chemical and physical specifications.

A "clean" filter indicates a low level of hidden contamination whereas a tainted filter indicates a sizable amount of "background dirt," especially when particles are present.

For more on **nonsterile manufacturing,** consider checking out *Contamination Prevention for Nonsterile Pharmaceutical Manufacturing* in the PDA Bookstore (www.pda.org/bookstore)

Contamination can be hidden from the human eye. To ensure it is low, the hidden contamination level must be checked to compare different producers and their manufacturing processes. At present, no regulation is in place addressing particulate contamination for oral dosage forms, but the filter test is a good measure to compare the manufacturing process and quality of different manufacturers as part of GMP.

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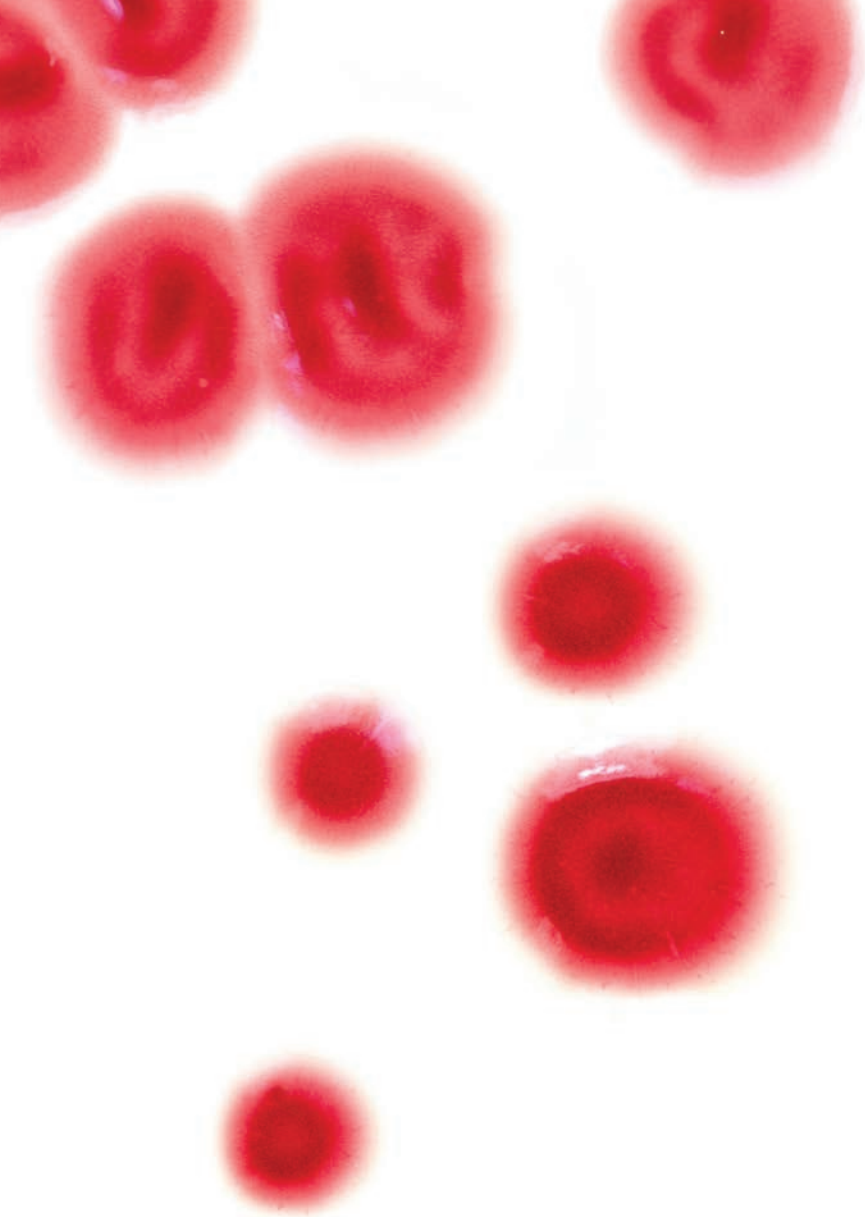
About the author

Annette Kirsch is head of the Global Analytical Technology Lab in the pharmaceutical division of Merck KGaA in Darmstadt, Germany.



Serratia marcescens **causes a broad range of infections including meningitis, pneumonia, and conjunctivitis.**

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Russian GMP Inspections Present Challenges: Part II

Vladislav Shestakov, Russian State Institute of Drugs and Good Practices, and Elizabeth Meyers, Amgen

[Editor's Note: Part I was published in the October *PDA Letter*.**]**

The Russian GMP inspectorate performs a vast array of activities. A substantial portion of these involves integrating Russia into the global pharmaceutical community, participating in development of a regulatory framework for the common pharmaceutical market among Eurasian Economic Union (EAEU) member countries and creating an international independent expert board of inspectorates. This last project, the most promising, entails establishing trust in the inspectorate. The increased number of inspections and mutual GMP recognition should decrease the burden on pharmaceutical manufacturers, substantially improving the quality of production.

Implementing good practices and working with experts in the pharmaceutical industry to create a professional system of values is another important goal of the Russian GMP inspectorate. The Federal State Institute of Drugs and Good Practices (SID & GP) is making a determined effort to support Russia's integration into the global pharmaceutical community. To that end, harmonizing EAEU legislation with global best practices and gaining accord with EAEU member state inspectorates to PIC/S remain high priorities.

The EAEU intends to create a common market of drugs. In December 2014, Russia, Belarus and Kazakhstan signed the Agreement for Unified Principles and Rules of Drugs Circulation within the EAEU. Armenia and Kyrgyzstan entered into the agreement in 2015. A number of important measures are covered by this agreement, which applies to all countries within the EAEU territory, including:

- Implementing good practices at all steps of drug circulation
- Creating controls by means of pharmaceutical inspections
- Developing a common EAEU pharmacopeia

- Maintaining a key element of GMP compliance supervision—accreditation of qualified persons and maintaining a registry of them
- Establishing unified rules of registration, expert evaluation, etc.

In August 2016, during a meeting of the Eurasian intergovernmental council, leaders from Union member states approved the EAEU GMP, a set of documents regulating the field of drug circulation, which concurs with EU GMP. Creation of a common market for drugs recognizes the results of inspections conducted throughout the EAEU territory.

In this regard, all EU member states face major efforts to harmonize legislation, solicit experts, train inspectors, encourage good practices, create an inspectorate, access PIC/S and invest in technological advancement of the resource base for the testing of drugs, among others.

Implementation of a common inspection system within the EAEU territory is preceded by a transition period. Until the end of 2018, submission of a "national" document (i.e., the document issued by the national authority of an EAEU member state) is allowed for confirmation of compliance with GMP. Also, until that time, parallel inspections of manufacturers for compliance with EAEU GMP can be conducted for the purposes of registering drugs. By the end of 2020, manufacturers within EAEU member states will be able to confirm GMP compliance in two ways: by a document from EAEU and by a document issued by an EAEU member state's regulatory body.

Harmonization Issues

Even with availability of a robust, thoroughly controlled system of drug manufacturing, it remains impossible to control 100% of all pharmaceutical manufacturers worldwide. This is often due to varying approaches to GMP regulation in different countries. Throw in a multitude of ➤

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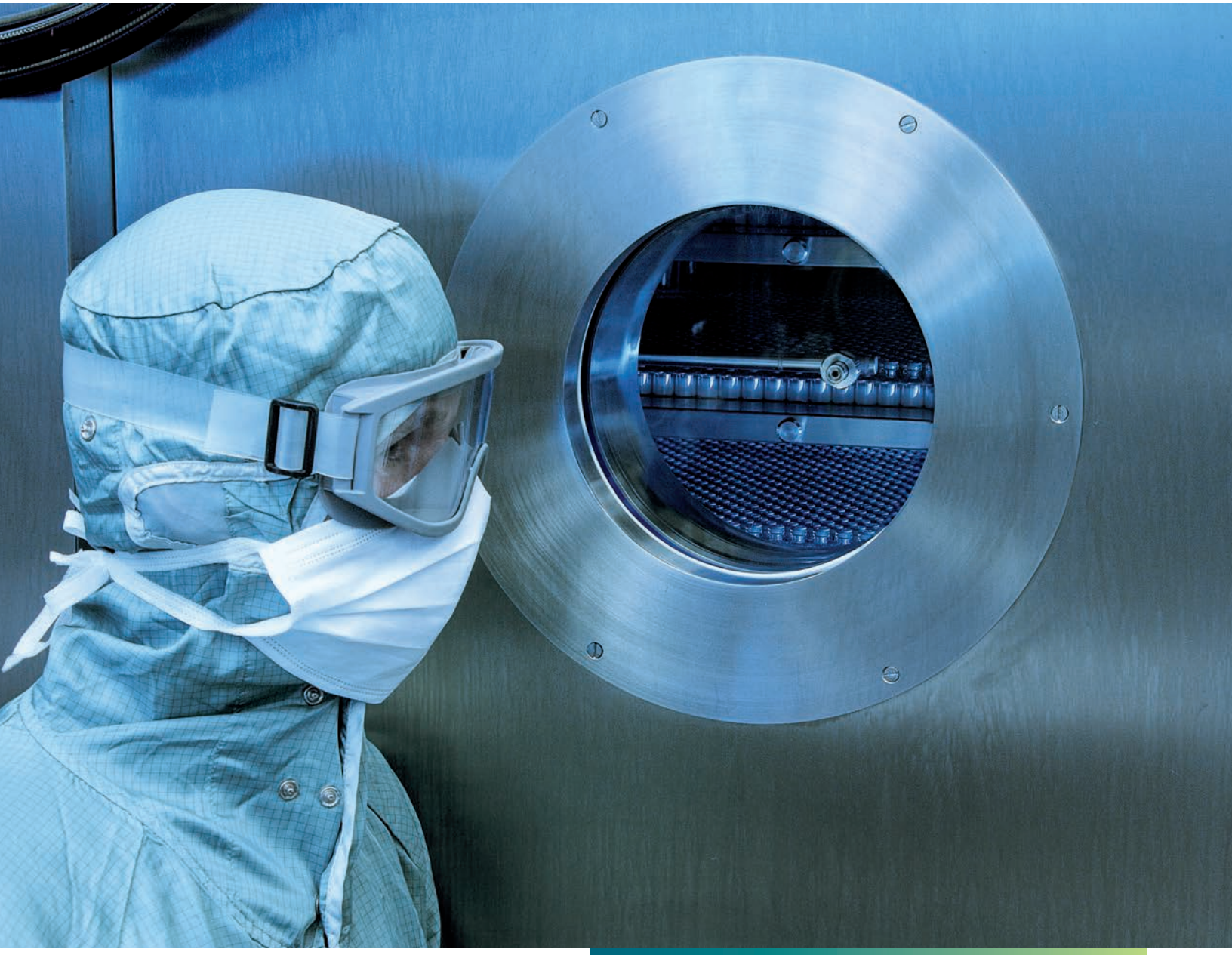

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national pharmacopeias and recognizing results of inspections in different countries can be complicated. For example, when entering new markets, manufacturers must be inspected repeatedly by various inspectorates.

There is a pressing need to reduce import/export barriers and harmonize approaches in addition to implementing mutual recognition of the results of inspections.

At the heart of developing GMP inspection standards in the EAEU region lie two major priorities: accession of EAEU regulatory bodies to PIC/S and harmonization of EAEU legislation with best global practices.

PIC/S Accession

All EAEU member states, except Kyrgyzstan, have attempted PIC/s accession. Belarus, Kazakhstan, Armenia and Russia have all submitted applications to join PIC/S.

Belarus, the most advanced country among the EAEU member states, is now in the process of joining PIC/S. With assistance from the European Union, the Belarus inspectorate developed its laboratory facilities and a structure for its pharmaceutical regulatory framework.

There is a pressing need to reduce export/import barriers and harmonize approaches

In support of its PIC/S application, Kazakhstan implemented organizational changes within its pharmaceutical inspectorate along the model of the U.S. FDA. This inspectorate would report to the Ministry of Health. Inspections and expert evaluations of drugs would be carried out by a separate regulatory body.

Armenia also has plans to reorganize its pharmaceutical regulatory framework. A regulatory agency is expected to be created soon that would report directly to the prime minister of the country. This agency would be responsible for carrying out inspections, issuing registration dossiers and providing expert evaluation of drugs and medical devices, much like the FDA.

Kyrgyzstan has not attempted to access PIC/S, although they plan to form an inspectorate similar to that of Kazakhstan. As the pharmaceutical market in this country is rather small and there are only a few pharmaceutical manufacturers, the number of inspectors will be limited.

Finally, Russia submitted a PIC/S accession application in August 2017. Now, major efforts are being made to harmonize the regulatory approaches. The SID & GP inspectorate was pre-audited by an independent party for compliance with PIC/S requirements and found that all internal ➤

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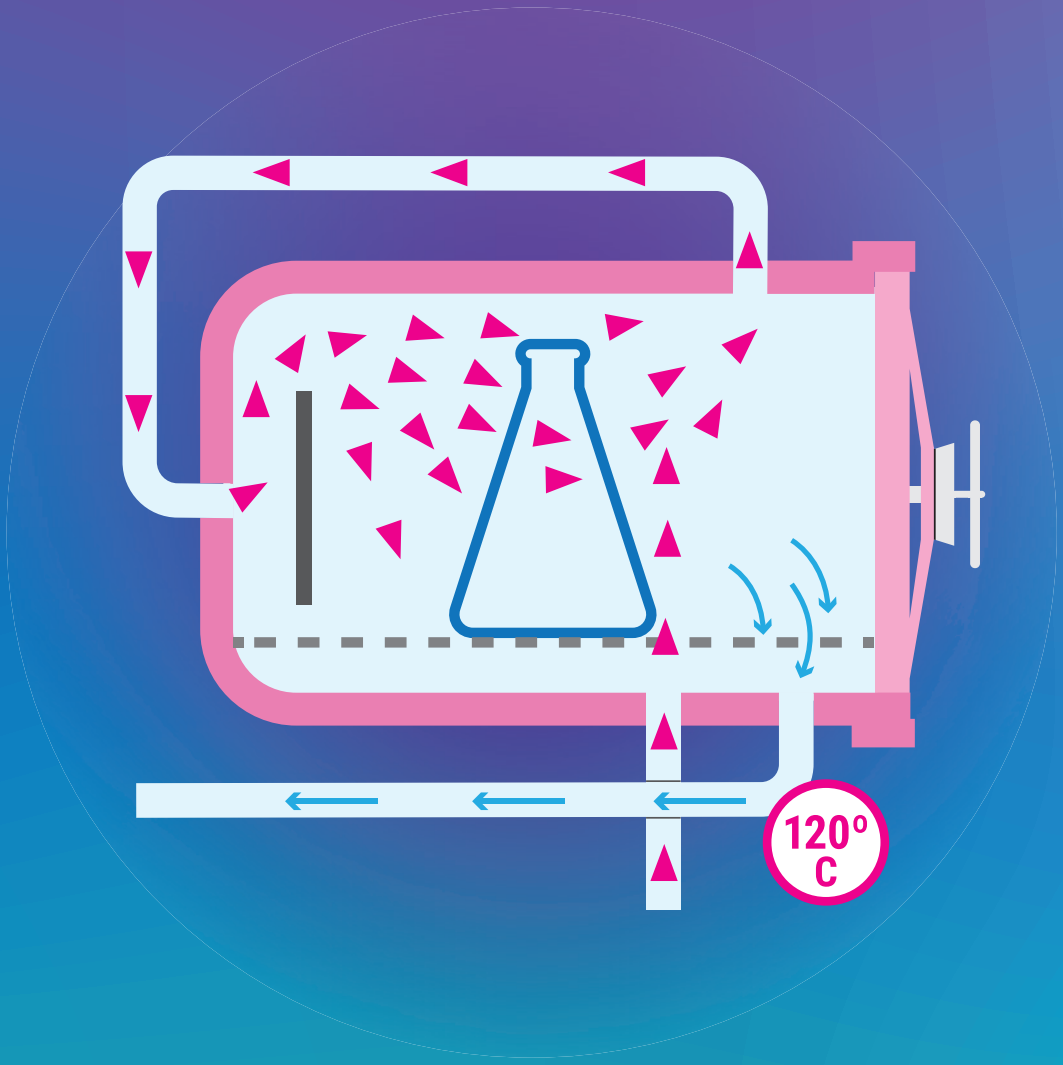

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documents comply with the PIC/S requirements. To implement the plans for PIC/S accession, however, it will first be necessary to amend federal legislation.

Harmonization within the EAEU

Toward the end of 2016, EAEU member states approved the standards and principles of its shared common pharmaceutical market. And on Nov. 3 of that same year, they signed the documents that would regulate that market, including:

- Rules for registration and expert evaluation of drugs
- Good pharmaceutical practices in the sphere of drug circulation
- Rules for carrying out pharmaceutical inspections
- Procedures for carrying out joint pharmaceutical inspections
- General requirements for the quality system of pharmaceutical inspectorates

Six key challenges to harmonization have been identified:

1. The need for further advancement of joint GMP regulation in EAEU countries
2. Establishment of unified approaches to regulation and positions in inspection issues, both internally and globally, for carrying out inspections, classifying nonconformities and developing educational standards and training programs for inspections
3. Cooperation of inspectorates (carrying out joint inspections, conducting joint training sessions, consulting on applying GMP regulations)
4. Drawing up recommendations for EAEU member states' inspectorates
5. Initiation of improvements of GMP regulations under a simplified procedure in relevant EAEU authorities
6. Exchange of inspection reports and creation of a unified base of such reports

Based on a meeting of the Eurasian Economic Commission held Nov. 16–17 2017, a decision was made to create a standing Pharmaceutical Inspections Committee within the EAEU. This committee will facilitate:

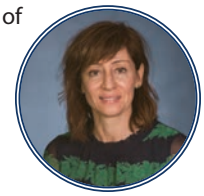
1. Strengthening of trade, economic and professional relationships among EAEU member states
2. Cutting disreputable manufacturers from the market
3. Increasing drug safety by improving the quality of manufacturing
4. Creating conditions to increase export opportunities
5. Enhancing the quality of inspections
6. Promoting transparency in mutual GMP recognition issues
7. Reducing requirements on pharmaceutical manufacturers

EAEU rules and procedures were initially developed based on PIC/S requirements. Currently, a working group is being formed within the Eurasian Economic Commission to address conducting pharmaceutical inspections for compliance based on good pharmaceutical practices. The working group first met Feb. 1, 2018, with plans to hold monthly briefing sessions and expanded quarterly sessions. The group is tasked with coordinating activities and harmonizing and developing procedures and methods (i.e., detailed SOPs).

The Russian inspectorate was formed and developed relatively recently. While 2018 marks only its third year of inspecting pharmaceutical manufacturers, the inspectorate plays an essential role in the Russian regulatory system. Inspections of foreign manufacturers have uncovered many findings, making clear the need for harmonization. The Russian inspectorate maintains an open dialog with industry and leads the way for creation of unified inspectorates in the EAEU.

About the Authors

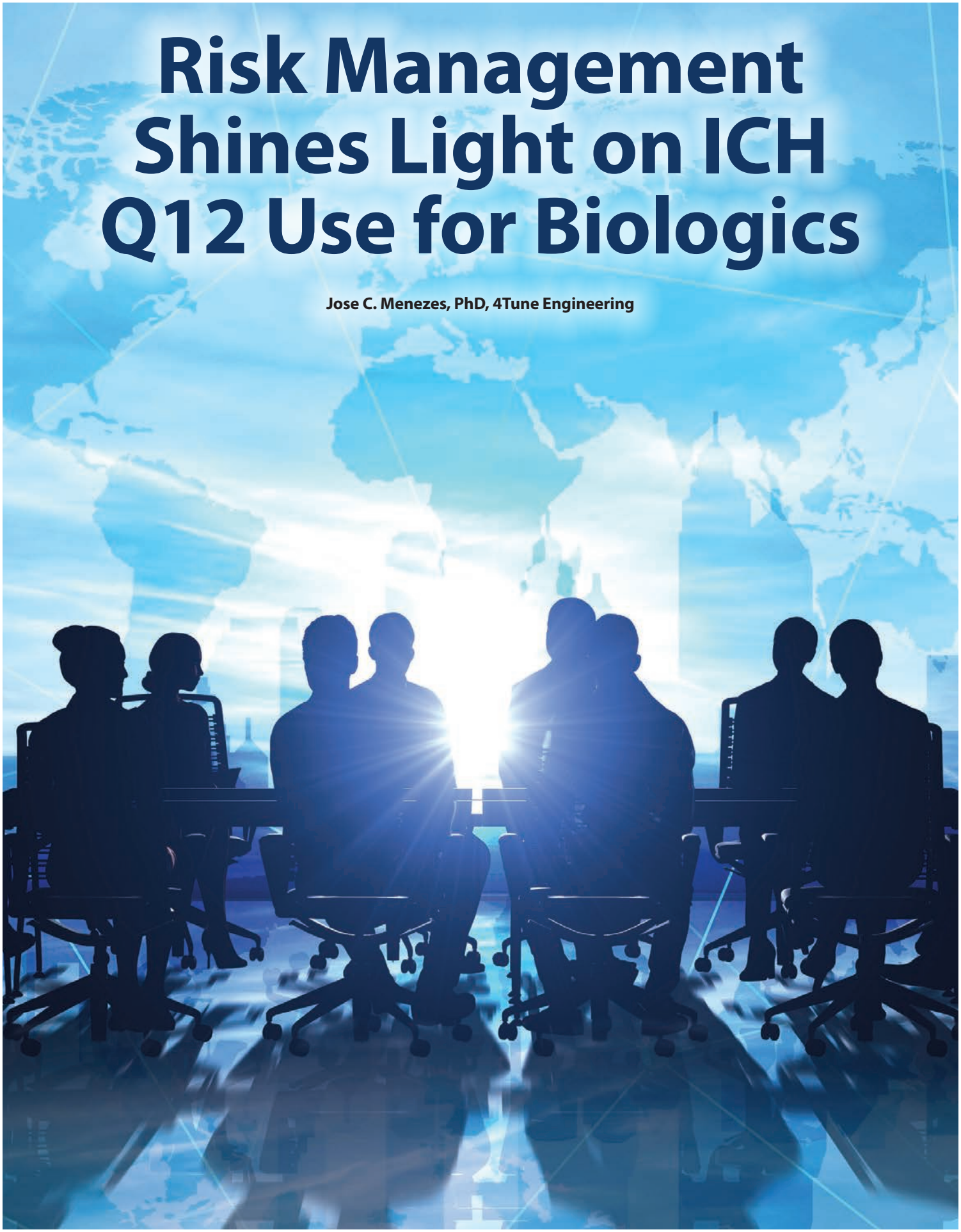
Vladislav Stestakov is Director of the Russian State Institute of Drugs and Good Practices under the Ministry of Industry and Trade of Russian Federation (MoIT). He is also a certified international WHO GMP inspector.



Elizabeth Meyers is a Director of International and Distribution Quality at Amgen. Prior to joining Amgen, she worked as an analytical chemist in both the United States and Russia. She is a member of the PDA RAQAB (Regulatory Affairs and Quality Advisory Board).

Risk Management Shines Light on ICH Q12 Use for Biologics

Jose C. Menezes, PhD, 4Tune Engineering



Wanting pharma companies to consider quality-by-design (QbD) elements throughout a product's entire lifecycle, including post-approval changes, through integration of risk- and knowledge-based approaches, seems to have become a global regulatory expectation. For biologics, however, using these approaches is more complex and companies cannot simply adopt the same strategies used for traditional small molecules.

Take, for example, a monoclonal type of biologic: counting all the combinations of post-translation modifications, the number of potential critical quality attributes (pCQA) is in the range of 285 million. Then, compound that with all the other pCQAs related to structural and activity attributes. Clearly, only a fraction are clinically relevant; at present it is not possible to measure all those pCQAs to determine their criticality. For this reason, a tiered approach, involving a science-/evidence-based evaluation must be balanced with a risk/residual uncertainty evaluation.

New concepts have been introduced that are not solely specific to the large-molecule field

One step in this direction is the set of U.S. FDA documents on similarity assessments, which cover a risk-based, tiered approach to ranking the clinical relevancy of residual uncertainties ***(1,2).*** FDA coined the term "Totality of Evidence" for the combined evaluation of the complete bioanalytical package that, together with the clinical package, establishes a stronger foundation and links between quality, safety and efficacy.

Still, it is only now becoming possible for companies to capture the level of sophistication in risk and knowledge management needed to include QbD elements **(Figure 1).** In the words of **W.E. Deming,** "knowledge has a temporal dimension" related to the experience a company gains over a product's lifecycle (past) and uses for its current actions and decisions (present) to better control and improve its technology platforms and portfolio products (future).

ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* provides, to a large extent, the means for companies to formalize their knowledge assets in terms of quality commitments (e.g., "established conditions" concept), and require an end-to-end lifecycle view of all its operations, identifying risks and categorizing types of changes. ICH Q12 also proposes PAC management protocols (PACMP) for each type of PAC and encourages rigorous science- and risk-based decisions.

The bottom line? ICH Q12 has yet to be fully realized. In theory, a company ➤

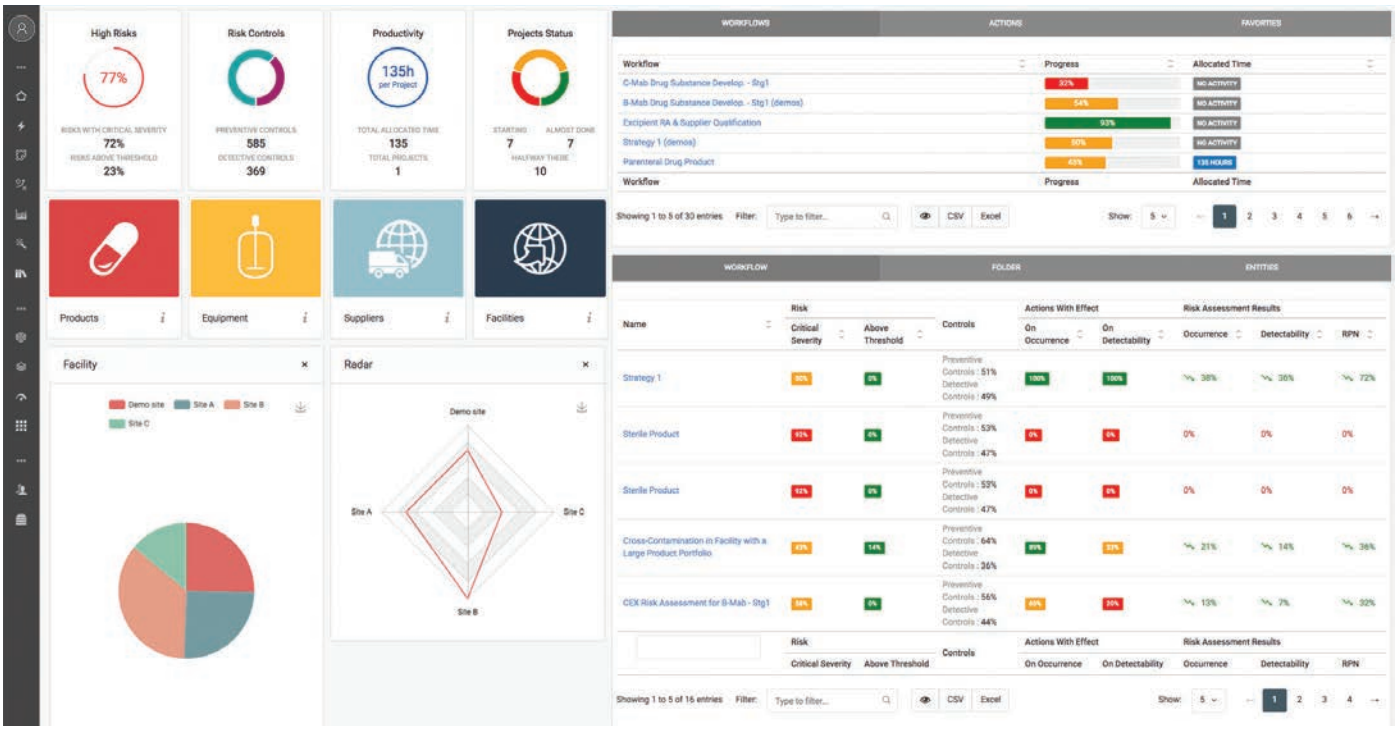


Figure 1 The Integrated Use of Different Risk Management Tools (*shown in what could be called standardized workflows or templates that inherit causality and attributes from objects that represent the whole process being analyzed end-to-end and over the product lifecycle*) ***(1)***

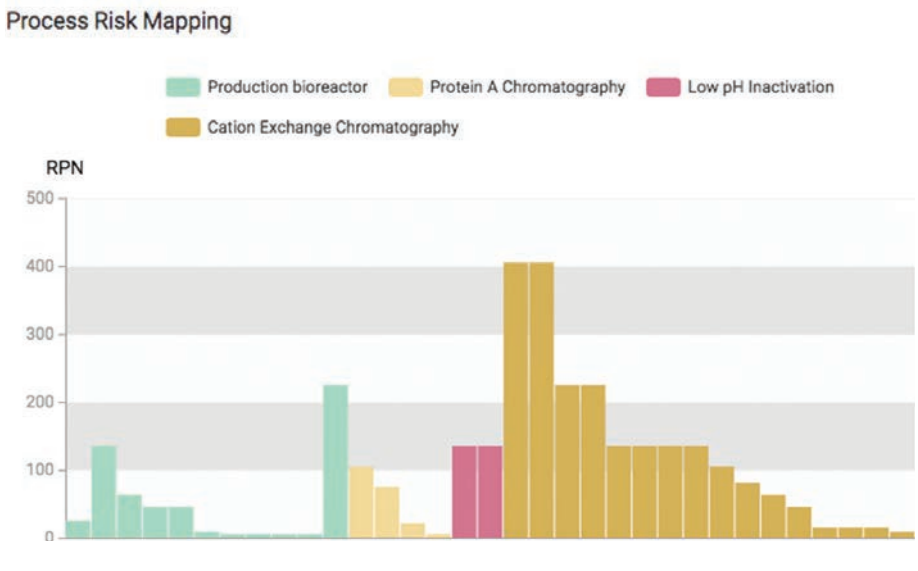


Figure 2 Different Aspects of the End-to-End and Lifecycle Management Oversight of Risks in Biological Process/Product (*Figure details an overview of failure modes on and end-to-end FMEA in a biological process with full traceability to process location and the description of the failure mode itself.)*

following ICH Q12 within a modern and robust pharmaceutical quality system will be granted greater regulatory flexibility than companies without clear evidence of quality culture excellence **(Figures 2–3).**

QRM, used in that way (i.e., within a lifecycle management framework), is an effective way to ensure consistency at all levels of modern pharma operations. This is the way forward toward a paradigm of Industry 4.0 rooted in a culture of quality and operational excellence. That is the vision of Class A organizations or, in short, "learning organizations" ***(3).***

Conclusion

Biopharma is entering a new and exciting era in which the type of practices used are no longer those inherited from traditional small-molecule manufacturing. New concepts have been introduced that are not solely specific to the large-molecule field but also intentionally address the inherent complexity of biologics. That is reassuring at a time the industry is launching new modalities that depart from the classical antibody model. And, as a result, a new science—

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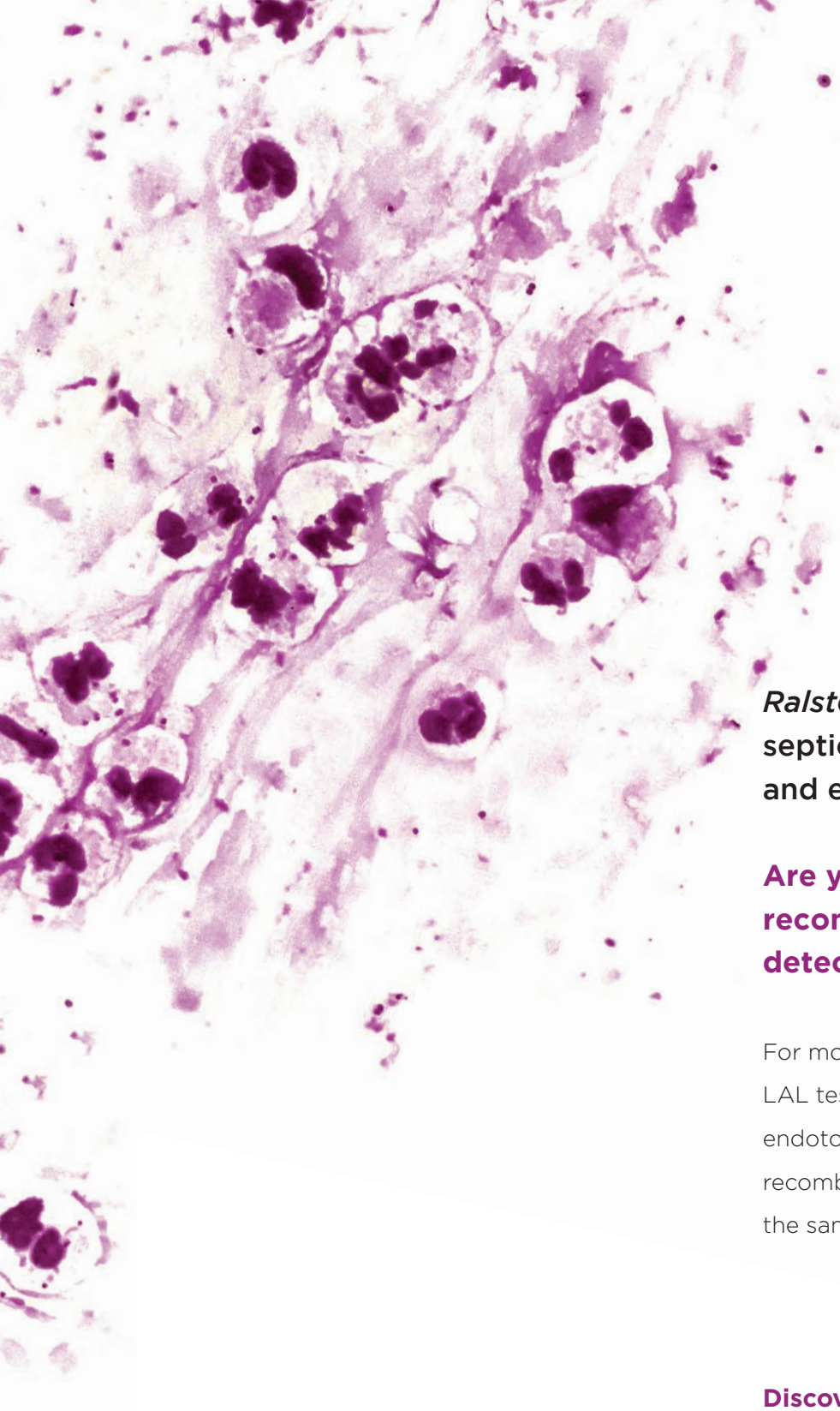

Ralstonia pickettii **can cause septic arthritis, osteomyelitis, and even death.**

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Thanks for the Warning Letter: Part I

When it Takes a Warning Letter to Spur Company Action

Steven Lynn, Lynn Consulting, LLC

In the not-too-distant past, I was driving to downtown Washington, D.C. on a rainy morning in September. After fighting the tortuous traffic, I finally arrived at the *PDA/FDA Joint Regulatory Conference*. My first order of business? Find that life-sustaining cup of coffee. After checking in, I made a beeline to the coffee stand.

After pouring the wonderous elixir, I turned around to see a gentleman patiently waiting to speak to me. He introduced himself as the quality head for a pharma company and asked me to step over to a quiet corner to talk. As we walked over to the corner, I quickly realized that I had just sent his company a warning letter a few months back. I expected him to simply give me the normal quick update on the remediation process. So, I took a swig and waited for his update. Then, the gentleman said five words that almost made me spit my coffee out.

"Thanks for the warning letter."

After a hard swallow, I was able to get out a one-word reply, "Why?" After all, why would someone thank me for sending them a warning letter? Has this gentleman gone completely bonkers?

Some background, I am the former Director of the U.S. FDA's pharmaceutical Office of Compliance. In this role, my colleagues and I were responsible for the CGMP oversight of all drugs manufactured in and/or imported into the United States. One of my many responsibilities involved approving, signing and sending warning letters to noncompliant companies. During my tenure, I unfortunately sent many warning letters. I say "unfortunately" because I received no pleasure in this activity as the issues I noted could often have been prevented.

In this two-part article, I aim to stir things up, ask some tough questions and create a healthy dialogue. The opinions and ideas are my own. They are ideas I have amassed throughout my career in the public and private sectors. I do not profess to have solutions to these complex problems. The solutions will not come from one individual. It is going to take all of us, which is why I wrote this article—to keep the dialogue going and, hopefully, catalyze more action. We cannot accept the status quo. It is not sustainable. Do you truly think the status quo in our industry is acceptable, and the patients we serve are getting what they need and deserve?

Let us begin with some background. What is an FDA warning letter? Chapter 4 in the Regulatory Procedures Manual (RPM), which is available on the FDA website, explains this. A warning letter is the "Agency's principle means of notifying regulated industry of violations and achieving prompt voluntary correction." While FDA uses this as a principle tool, the RPM goes on to note that a warning letter is "informal and advisory" and "communicates the Agency's position." It is not, however, a tool that is used hastily. FDA takes issuing a warning letter very seriously; a great deal of deliberation goes into the final decision to issue one. In turn, if a company receives a warning letter, they need to take it just as seriously.

A warning letter essentially tells a company that FDA has observed "violations of regulatory significance." Significant violations are further detailed, as those violations "may lead to enforcement action if not promptly and adequately corrected." When a company receives a warning letter, FDA expects the company to come into voluntary compliance within a reasonable time frame. If they do not perform the necessary corrections, FDA can, and will, move to more stringent actions, for example, an injunction, or, what I call, a court-ordered quality improvement plan. A warning letter is just one way FDA puts a company on notice that they have serious problems to fix. For this reason, FDA typically sends the warning letter to the most senior leader in a company (e.g., the CEO) to ensure that proper attention will be paid to preventing and fixing the noted violations.

Many different variables feed into the warning letter decision-making process. If you are interested to learn more, I encourage you to read through the RPM (www.fda.gov/iceci/compliancemanuals/regulatoryproceduresmanual/).

Back to that thankful gentleman at the *PDA/FDA Joint Regulatory Conference.* I asked him why he said thank you. He explained that he and his operations and-manufacturing colleagues had been trying to escalate their mounting problems to top leadership for quite a while, but the C-suite leaders did not take notice until the warning letter arrived on the CEO's desk. Now that the CEO and his direct reports had been made aware, proper attention and resourcing was being directed to correct and mitigate the problems.

It is a sad-but-true scenario in our industry. I did not make up this story; in fact, other quality and operations leaders have said these same five words to me.

So, what can we as an industry do? How can we ensure our executives understand, know and appreciate the value of a robust pharmaceutical quality system? How do we ensure that, from the top of the organization to the line-level workers, our colleagues fully grasp the fact that quality is everyone's job? How can we ensure a robust pharmaceutical quality system?

The answer: It depends. It depends on the pharmaceutical company and its organizational quality culture. What I mean is, each organization has to have an ingrained culture of how it does what it does. While the concepts and principles of quality are similar across the industry, the ways of implementing them within each company are nuanced based the culture of the individual company. Also, how to get and keep the CEO, Board and execu-

tive teams focused on quality is different for each company based on its particular culture. This is a complex conundrum that many great minds are trying to solve. For example, PDA has task forces on quality culture, quality metrics, post-approval changes, etc. Other organizations across our industry have other endeavors in progress, as well, to help improve our industry. As I noted above, no one individual has all the solutions.

The famous quality guru **W. Edwards Deming** once said: "94% of all failure (in an organization) is a result of the system…not people" and that "the basic cause of sickness in American industry… is failure of top management to manage." I would expand upon this last quote and say the failure is not just with American industry, but with global industry, because Deming made these statements decades ago, before the advent of the globalized society that is our current reality.

About the Author

Steve Lynn is currently a consultant. Previously, he worked for Novartis, Mylan and the U.S. FDA, where he led multiple major domestic and international drug programs designed to assure compliance with CGMPs.

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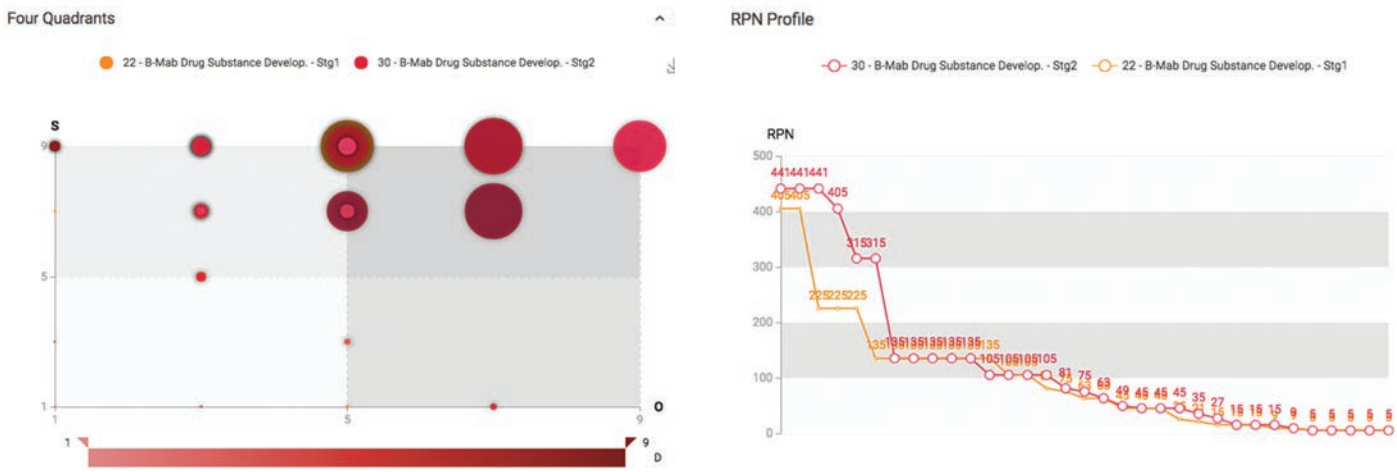

Figure 3 A Comparison of Risk Profiles Before/After a Process Change is Implemented, Allowing Risk-Based Justifications in Post-Approval Submissions

one able to quantitate the explicit parts of both evidence- and risk-based components and accept noncritical uncertainties—has emerged.

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About the Author

Jose C. Menezes has been director of a program in Pharmaceutical Engineering covering QbD and PAT at the Technical University of Lisbon since 2007. He has published extensively on these subjects (80 papers and 3 books). He is founder and CEO of 4Tune Engineering Ltd, an award-winning company, working in the areas of MS&T and QRM with large biopharma companies for more than a decade.

Science Advisory Board Closes on a Jam-Packed Year

Ghada Haddad, Merck & Co.

This year has been both challenging and rewarding for PDA's Science Advisory Board (SAB). A number of projects are underway that support the advancement of science in the industry and growth in manufacturing innovations.

One of these efforts is the Manufacturing Science and Operations Program℠ (MSOP), which aims to:

- Highlight PDA's ongoing focus on pharmaceutical and biopharmaceutical manufacturing
- Build practical solutions by filling known gaps in current manufacturing science along with any gaps that become apparent based on continuing developments
- Encourage new manufacturing technology and methods

Potential deliverables within this program include: industry surveys, points-to-consider papers and other technical documents, educational programs, workshops, etc. Two new projects have already been balloted, so stay tuned for more news in this area **[Editor's Note:** see "PDA Forms New Big Data Task Force," on p. 11 to learn about a new MSOP℠ task force**.]**

SAB has also actively voted on seven technical ballots, supported 12 interest groups and ensured EU and U.S. interest group leaders are in place. Speaking of interest groups, there has been an increase in membership within the 12 interest groups falling under the SAB umbrella. All SAB interest groups are now on PDA Connect℠. I encourage you visit PDA Connect℠ (community.pda.org) and participate in one.

In addition, SAB released several technical publications of interest to the industry: *PDA Technical Report No. 79: Particulate Matter Control in Difficult to Inspect Parenterals*, a glass quality survey, the *PDA Journal of Pharmaceutical Science and Technology* article, "Achieving 'Zero' Defects for Visible Particles in Injectables," and more. SAB also initiated projects to develop documents around isolators and vaporized hydrogen peroxide (VHP) and is currently working to develop task forces for those topics. And, of course, SAB members commented on the draft Annex 1 revision.

As 2018 comes to a close, SAB says goodbye to the following members—**Jette Christensen, Don Elinski** and **Norbert Hentschel**—and thanks them for their contributions throughout their tenures.

As for new members, SAB welcomes **Chris Ames** from Akebia Therapeutics, Inc. He has been an active volunteer for the PDA New England Chapter and has worked on some of PDA's signature conferences and task forces. **Marcia Baroni** from Eli Lilly is also joining SAB. She has also been very active in PDA and is an expert in isolator/VHP technology, frequently speaking at global meetings. **Leo Xu** from Merck was appointed by SAB Chair **Maik Jornitz** and Co-Chair **Phil DeSantis** to join the SAB family, strengthening the link between SAB and MSOP℠. Not only has he been a very active member of PDA, but he is also leading an MSOP℠ initiative on predictive maintenance.

It has certainly been a busy year for SAB and, no doubt, 2019 will be just as busy if not busier. I encourage anyone who is interested in any of the initiatives mentioned to contact PDA's Volunteer Coordinator at volunteer@pda.org.

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