People • Science • Regulation

PDA Letter

Volume LII • Issue 5 www.pda.org/pdaletter May 2016

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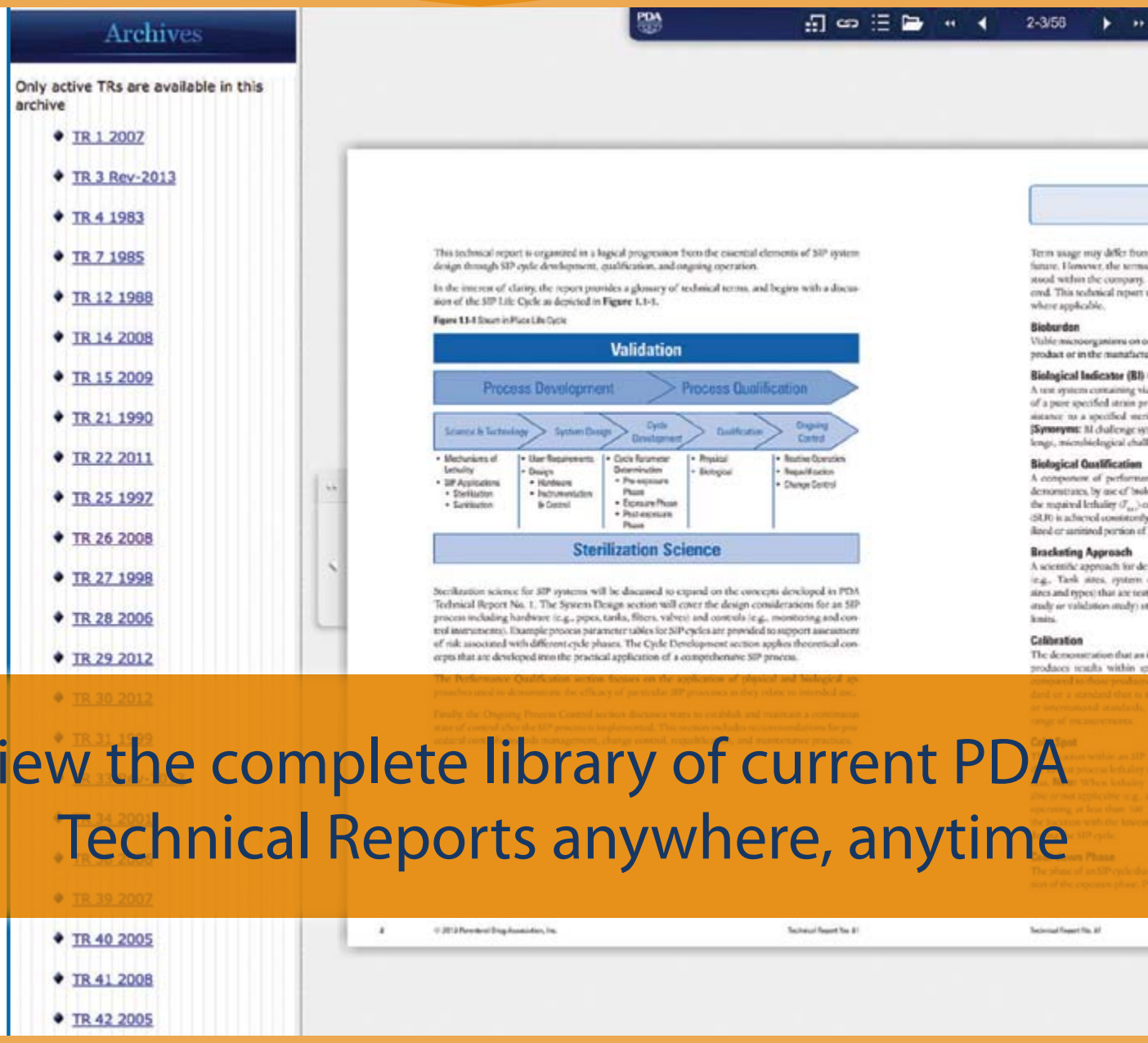
PDA's Technical Report Portal



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In today's drug product development laboratories, the pre-filled syringe remains one of the most popular primary container systems under development and the focus of much innovation, including new materials, modifications to existing materials, new devices, and new safety and connectivity features.

Which of this expansive array of innovative options should be implemented? How? And when? What new innovation will enable or expedite product development or differentiate an existing product? How should you address concerns about manufacturing, outsourcing, patient experience and patient data? Get answers to these and other questions from industry and regulatory experts at the *2016 PDA Universe of Pre-filled Syringes and Injection Devices*.

For more information and to register, visit pda.org/2016prefilled.

Immediately following this event, PDA will host the *2016 PDA Drug Delivery Combination Products Workshop* where you can hear pharmaceutical and medical device professionals share the challenges they have had or are currently facing. Interact with the participants in panel discussions on the issues that are important to the success of your product and company in the future!

Learn more and register at pda.org/2016combo.

And, on October 20-21, PDA's Education Department will hold two courses complementing what you have learned:

- *Understanding and Addressing Technical, Quality, and Regulatory Challenges for Drug Delivery Combination Products* (October 20)
- *Essential Elements of Extractables and Leachables: From Material Extraction to Final Report* (October 21)

Learn more and register at pda.org/2016PrefilledCourses.

#2016prefilled

PDA Letter

Volume LII • Issue 5 www.pda.org/pdaletter

Cover

26 Big Data Meets Vaccine Manufacturing
Rebecca Stauffer, PDA

Since the late 2000s, "Big Data" has become a buzzword used throughout various industries. The term itself refers to datasets "so large and complex that they become awkward to work with using standard statistical software" ***(1)***. Big Data is about more than just the collection of data. It's about using it to make decisions based on efficient analysis. Making sense of it is the challenge facing most companies. But companies are solving this challenge and taking specific actions based upon the information gained.

Cover Art Illustrated by Katja Yount

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Nanda Subbarao, Biologics Consulting

As a consultant, I have personally observed how method variability is often underestimated in pharmaceutical laboratories. This can lead to misinterpretations of data presented in the CMC. Such underestimations of variability should not occur in laboratories with robust overarching quality systems that cover all facets of a pharmaceutical laboratory's operations. Yet, in practice, I have seen quality systems breakdown for various reasons during routine laboratory operations, mostly due to limitations of time and resources.

34 The Economics of Vaccines

This issue's Infographic showcases some economic facts about vaccines.

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.

And the Winner Is!

Honor Award winners are those members whose contributions have most helped PDA fulfill its mission. Among the thousands of volunteers who work with PDA, these honored members are recognized for exceptional dedication and years' of service at the PDA Awards Dinner during the Annual Meeting. PDA congratulates and thanks the following recipients.

Honorary Membership

This is PDA's most prestigious award, conferring lifetime membership benefits to the recipient. The award has traditionally been given in recognition of long service that is significant in nature to PDA and requires unanimous approval of the PDA Board of Directors.

Robert Dana

Gordon Personeus Award

Presented in memory of the late **Gordon Personeus,** a past PDA President and long-time volunteer, this award honors a PDA member other than a Board member for long-term acts or contributions that are noteworthy or of special importance.

Katsuhide Terada **Wenzel Novak**

Frederick J. Carleton Award

This award is presented as a tribute to lifetime contributor, past President, past Executive Director and Honorary Member **Frederick J. Carleton,** and designated for past or present Board members.

Maik Jornitz

Packaging Science Award

This award is given in recognition of extraordinary contributions to PDA and the packaging science.

Dana Guazzo

Distinguished Service Award

This award is given in recognition of special acts, contributions or services that have promoted the success and strength of PDA.

Bettine Boltres **Robert Darius** **Anil Sawant**
Monica Caphart **Matthew Ostrowski**

Martin VanTrieste Pharmaceutical Science Award

Established in honor of long-time contributor and Chair-Elect **Martin VanTrieste,** this award is given annually for outstanding contributions to the advancement of pharmaceutical science.

Anthony Cundell

PDA Europe Service Appreciation Award

This award is presented annually for special acts, contributions or services that have contributed to the success and strength of PDA's European activities.

Renaud Janssen

Service Appreciation Award

This award is presented annually for special acts, contributions or services.

Melba Clavell **John Holmgren** **Sanjay Singh**
Ian Elvins **Rachel Karpel** **Lisa Skeens**
Gabriele Gori **Alice Redmond** **Sabrina Ullah**
Jeff Hargroves **John Shabushnig** **Anders Vinther**

James P. Agalloco Award

The James P. Agalloco Award is presented annually to the PDA faculty member who exemplifies outstanding performance in education. The award is named for **James P. Agalloco,** in honor of his work in developing the PDA Education program.

Wayne Garafola **Maik Jornitz**

Michael S. Korczynski Award

Established in recognition of contributions made toward the development of PDA's international activities by **Michael S. Korczynski,** PhD.

Stephan Rönninger

Frederick D. Simon Award

The Frederick D. Simon Award is presented annually for the best paper published in the *PDA Journal of Pharmaceutical Science and Technology.* This award is named in honor of the late **Frederick D. Simon,** a former PDA Director of Scientific Affairs. This year's award went to six recipients for their contribution to the article, "Manufacturing of High-Concentration Monoclonal Antibody Formulations via Spray Drying—the Road to Manufacturing Scale," which was published in the January/February 2015 issue of the PDA Journal.

Mayumi Bowen **Ada Hui** **Oliver B. Stauch**
Benson Gikanga **Yuh-Fun Maa** **Robert Turok**

Distinguished Editor/Author

This award recognizes the author or editor selected by PDA members for their contribution to PDA's technical books.

Tim Sandle **R. Vijayakumar**

President's Award

This award recognizes a PDA staff member, other than senior staff, whose exemplary performance has contributed to PDA's success during the previous year.

Faramarz Kolivand **Melanie Decker**

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

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PDA Volunteer Spotlight

John Holmgren

- Director, QA/QC and Validation
- *Allergan*
- Member Since | 2004
- Current City | Irvine, California

Membership opens your eyes to a vast amount of resources

Tell us about your experience volunteering for PDA's Southern California Chapter.

I have been involved with the chapter in many roles, including membership chair. I've just stepped down as chapter president as well. I've helped contribute with webcasts of chapter meetings across multiple sites, an annual industry summit, our *Nexus* newsletter, and the student chapter at the Keck Graduate Institute.

Why did you join PDA and start to volunteer?

I felt it was time to get involved with industry colleagues and gain a broader perspective of the pharma landscape.

What benefits do you get from volunteering with PDA?

It helps me stay in tune with "hot topics" in the industry that can lead to enhancements for my company's systems.

What do you like most about your PDA experience?

Having the ability to suggest key issues and bring industry experts to a local venue and discuss resolutions to problems.

What has been your favorite PDA Annual Meeting?

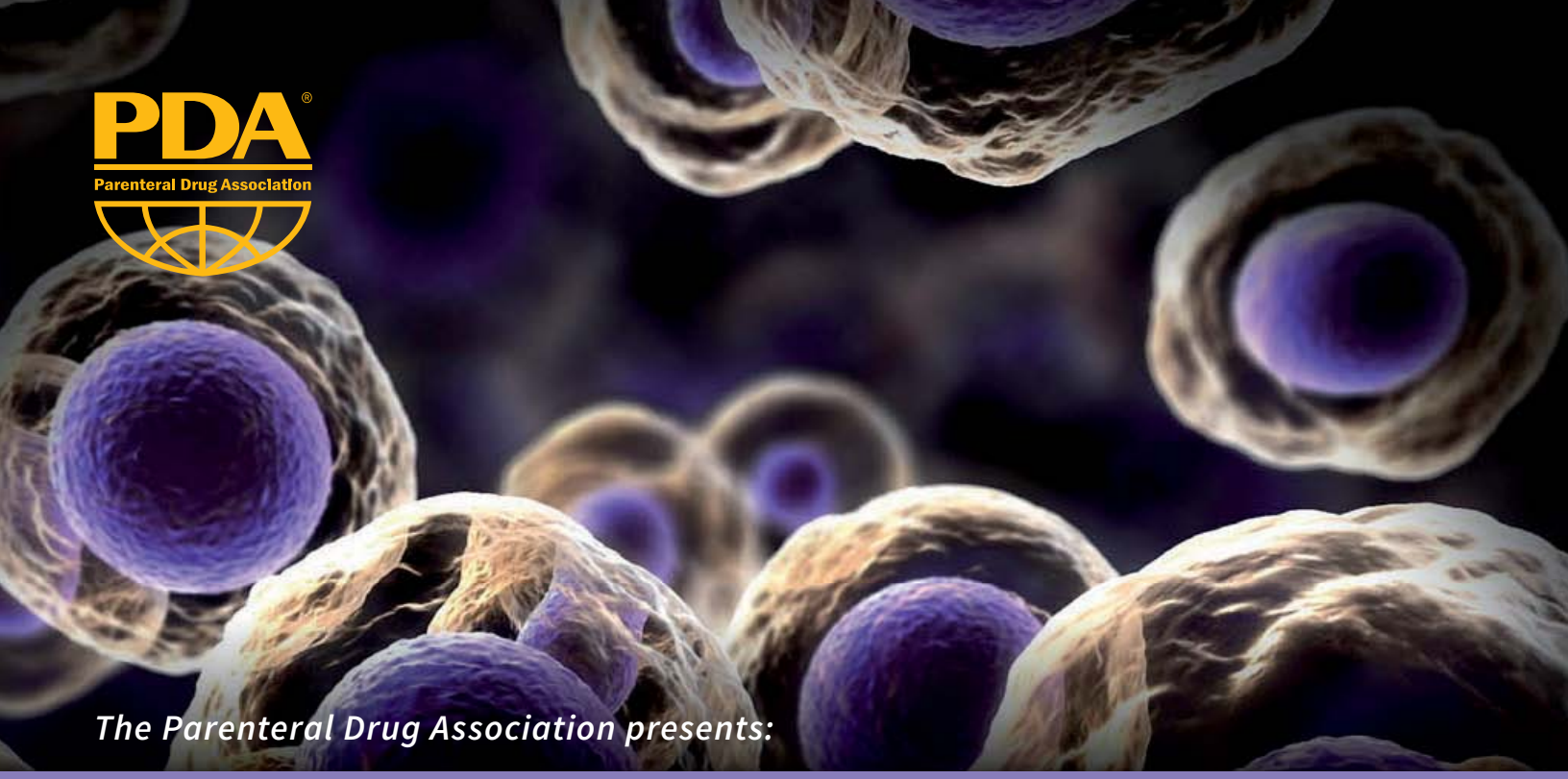
The 2008 annual conference in Colorado was memorable. It was a great location (Broadmoor Hotel), and I enjoyed the mountain scenery and snow.

What is an interesting fact about yourself?

I was born and raised in southern California. I attended UCLA and have spent my entire career with local companies.

What would you say to somebody considering PDA membership?

It opens your eyes to a vast amount of resources (subject matter experts, technical reports, publications, etc.) available to the entire industry and to a global point-of-view, so your access is no longer limited.



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Your Local PDA Connection

Are you curious about the issues unique to your region?

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

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

Ireland Chapter Recognizes Young Scientists' Work

Mike Morris, Irish Health Products Regulatory Agency (HPRA), PDA Ireland Chapter President

Last year, the PDA Ireland Chapter established a number of bursaries (i.e., scholarships) for students involved in the sciences. One of these bursaries was designated for second-level students participating in the BT Young Scientists and Technology Exhibition program organized by the telecommunications provider BT Ireland. As a result, the Chapter contacted schools participating in the Exhibition and invited student participants, particularly those focusing on the biological/life sciences, to submit their project titles and a short abstract to the Ireland Chapter's adjudicating committee. This Committee consisted of Chapter President **Mike Morris** and Chapter Committee member **Anne Greene.**

Of the 13 submissions received, the Committee recognized the work of **Emily Hamilton-Foott** and **Julie Giblin-Perrott** from Bandon Grammar School in County Cork as the best project. Their project investigated the level of mental health literacy among students attending a mixed gender rural school. The project's goal was to develop tools to educate students on mental health topics and understand terminology used for certain common conditions, such as depression, eating disorders and anxiety. Teacher **Moira Flynn** supervised the project. The Chapter found the project well-structured and well-planned within the time and resources available to the two students.

Greene and Morris met with Hamilton-Foot and Giblin-Perrott at the exhibition on Jan. 7 to discuss their project. The Chapter Committee awarded their school with a €200 scholarship to help defray the cost of the project. The two winners were given a PDA T-shirt printed by the Chapter. PDA T-shirts were also presented to the other participants in the chapter's competition. Greene and Morris met with many of the participants to offer them encouragement and support in the competition.

Emily Hamilton-Foott (left) and Julie Giblin-Perrott (right), the winners of the Ireland Chapter's scholarship competition, pose in their PDA T-shirts with Chapter President Mike Morris (center)

The Chapter was excited to support these young scientists in their endeavors and hopes to spread a positive message about the sciences and PDA as an organization.

PDA Who's Who

Moira Flynn, Teacher, Bandon Grammar School

Julie Giblin-Perrott, Student, Bandon Grammar School

Anne Greene, Lecturer, Dublin Institute of Technology

Emily Hamilton-Foott, Student, Bandon Grammar School

Mike Morris, Director, Scientific Affairs, Irish Medicines Board

+ 2016 PDA Annual Meeting

Plenary Sessions

Plenary 1: Putting the Patient First
(l-r) Dave deBronkart, Society of Participatory Medicine; Marina Kozak, PhD, Friends of Cancer Research

Opening Remarks
(l-r) Maik Jornitz, G-Con; Richard Johnson, PDA President, Martin VanTrieste, Amgen

Plenary2: Manufacturing and Supply Considerations to Enable Novel Therapies
(l-r) Ghada Haddad, Merck & Company; Michele Myers, GSK; Brian Urban, Biogen Idec; Tolga Musa, Biogen Idec

Plenary 3: Improving Efficiency and Reducing Manufacturing Cost
(l-r) Peter Carbone, Novartis; Glenn Wright, Eli Lilly; Matthew Shields, Amgen

Plenary4: Rapid Product Development
(l-r) Dorota Matecka, U.S. FDA; CAPT Sharon Thoma, PharmD, FDA; Earl Dye, PhD, Genentech

Plenary 5: Ensuring Supply of Medicines and Expanding Access
(l-r) Jeffrey Blue, Merck; Jayanth Sridhar, PhD, Cipla

A1: Achieving High Quality and Productivity in Cell Culture Processes

(l-r) Karen Walker, Novartis; Michael De Felippis, PhD, Eli Lilly; Louis Masi, FloDesign Sonics; Tongtong Wang, PhD, Eli Lilly

B1: Ensuring Supply by Using Multiproduct Facilities and Reducing Supply Chain Risk

(l-r) Nathalie Frau, PhD, Sanofi Biologics; Vijay Chiruvolu, PhD, Kite Pharma; George O'Sullivan, Kite Pharma

C1: Integrating New Technologies and Products

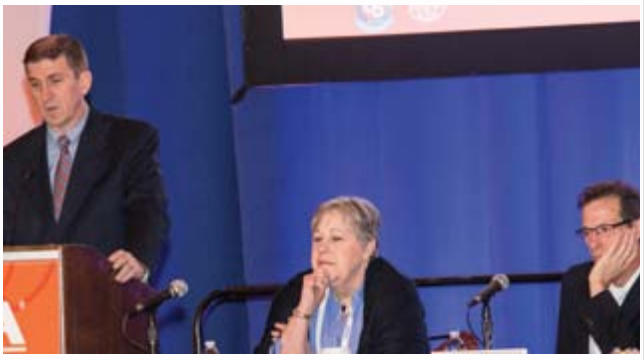
(l-r) Ranjit Thakur, Janssen; Greg Whitehead, blue bird bio; Hal Baseman, ValSource

A2: Challenges and Advances within Downstream Technologies

(l-r) Morten Munk, NNE Pharmaplan; Howard Levine, PhD, BioProcess Technology Consultants; Jeff Johnson, Merck

B2: Adapting Manufacturing Facilities

(l-r) George Wiker, AES Clean Technology; Ghada Haddad, Merck; Tsutomu Ota, Takeda



C2: Driving Continuous Process Improvement Through Effective Lifecycle Management

(l-r) Daniel Blackwood, Pfizer; Susan Schniepp, Regulatory Compliance Associates; Paul Motchnik, PhD, Genentech

2016 PDA Annual Meeting

Breakout Sessions

A3: Advances in Analytical Technologies for Microbial Control

(l-r) Johannes Reich, Hyglos; CAPT Sharon Thoma, PharmD, U.S. FDA; Sven Deutschmann, PhD, Roche

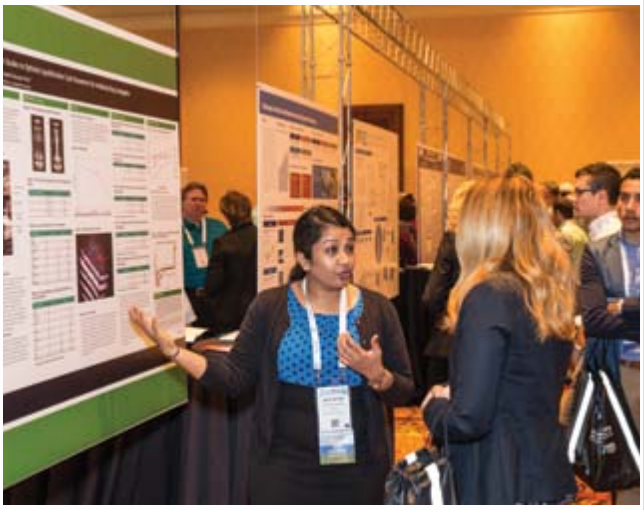
B3: Review of Single-Use Processing Equipment Experiences and Needs

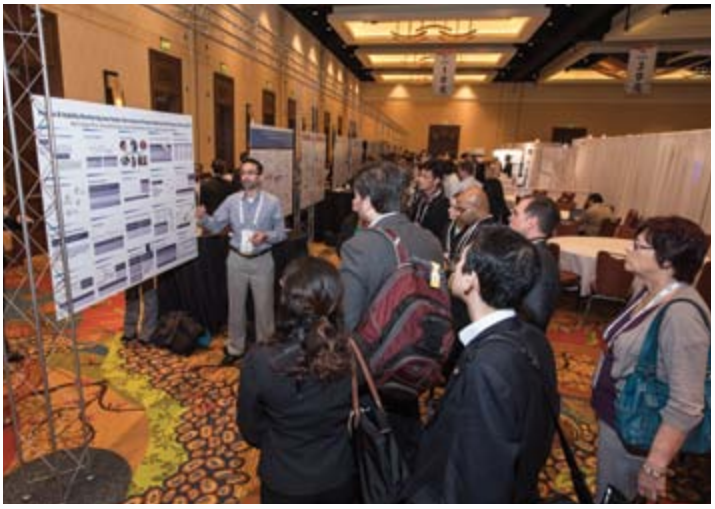
(l-r) Maik Jornitz, G-Con; Marc Hogreve, Sartorius; Haodi Dong, Wuxi Biologics

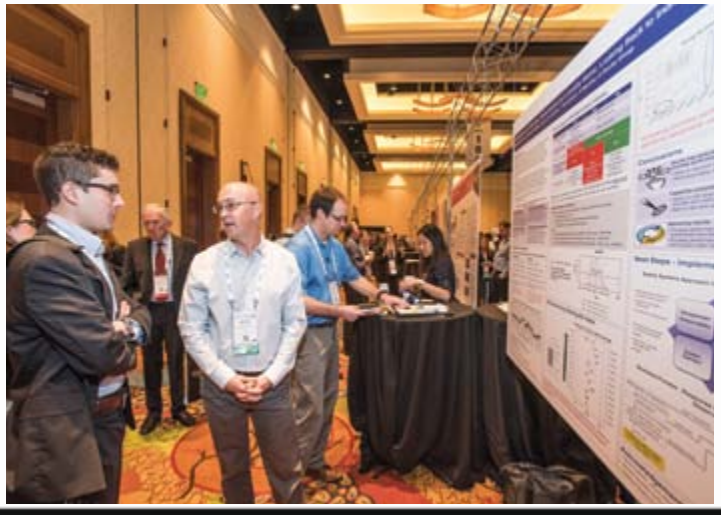
Walk/Run

Participants in the 10th Annual Walk/Run raised $6,850 for Fisher House Incorporated.

Poster Exhibit







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2016 PDA Annual Meeting

Exhibit Hall

Kelly Benesky won a Fitbit Surge from Lonza

CAI's Stephanie Gaulding presents Amnon Eylath with a smartwatch

Julie Wong receives an Amazon gift card from Novatek

Lillian Bell (far right) receives an Amazon Echo from representatives of Wako Chemicals

Blossom Smith won a Fitbit from Pace

Midi Labs awarded Karen Bossert Beats headphones

PDA gave Lisa Walters an Apple iWatch

BioAB Advances Ambitious Agenda

Rebecca Stauffer, PDA

In March, PDA's Biotechnology Advisory Board (BioAB) convened for a face-to-face meeting before the *2016 PDA Annual Meeting* to discuss BioAB's strategic initiatives. The biopharmaceutical segment of pharma is rapidly expanding so there were ample biotech-oriented topics to discuss. Currently, BioAB is focusing on three main areas: biopharmaceutical manufacturing, biosimilars and cell/gene/tissue therapies.

In the area of biopharmaceutical manufacturing, the latest advancments include continuous processing, which offers significant advantages to manufacturers and is openly supported by the U.S. FDA. BioAB's discussion of continuous manufacturing preceded by a few weeks the U.S. FDA's announcement that it had just approved the first batch-to-continous manufacturing process for Janssen Products' HIV-1 product. BioAB recognizes the growing importance of advanced manufacturing and will be involved with developing high-level guidance in the area. Look for sessions delving deeply into biopharma manufacturing at next year's Annual Meeting and for more articles on the topic in upcoming issues of the *PDA Letter*.

BioAB also discussed the upcoming *2016 PDA Biosimilars Conference* in Baltimore, which it has been supporting through participation on the planning committee. Another hot area BioAB continues to follow is cell/gene/tissue therapies. The upcoming ATMP conference in Berlin has transitioned to a more industrial focus (e.g., facilities, raw materials, container closure integrity, etc.). PDA recognizes that GMPs for ATMPs remain a major topic of concern for both industry and regulators.

BioAB also oversees the work of task forcess involved in the development of technical reports covering topics like reprocessing of biopharmaceuticals, standardization of mycoplasma filters and risk mitigation of virus contamination.

In addition, another BioAB task force is working on a key technical report on the Low Endotoxin Recovery (LER) phenomena.

BioAB is also reaching out to potential new members in Europe and seeking European co-leaders for the Biotechnology, Advanced Virus Detection Technologies and Vaccines Interest Groups. If you would like to assist the BioAB in any of its strategic initiatives and other projects, please contact **Josh Eaton** at eaton@pda.org.

Journal *Preview*

May–June PDA Journal Offers the Latest in Technological Applications in a Range of Areas

This issue's technology articles look at solutions for the capping process, media fills, determining glass vial quality and plasma decontamination. Could one of these articles outline a solution for your organization?

Research

T. Werk, et. al., "New Processes for Freeze-Drying in Dual Chamber Systems"

Paul Lopolito, et. al., "Cleaning and Disinfection of Bacillus cereus Biofilm"

Technology/Application

Roman Mathaes, et. al., "The Pharmaceutical Capping Process – Correlation between Residual Seal Force, Torque Moment and Flip-off Removal Force"

Derek Duncan, et. al., "The Application of Non-Invasive Headspace Analysis to Media Fill Inspection"

Yasser Nashed-Samuel, et. al., "Comparison of Acid Titration, Conductivity, Flame Photometry, ICP-MS, and Accelerated Lamellae Formation Techniques in Determining Glass Vial Quality"

Egmont Semmler, et. al., "Plasma decontamination: A case study on kill efficacy of Geobacillus stearothermophilus spores on different carrier materials"

Case Studies

Ting Shi, et. al., "Investigation of air-liquid-interface ring in buffer preparation vessels: the role of slip agents"

Commentary

Robin Payne, et. al., "A Roadmap for the Implementation of Continued Process Verification"

Tim Corbidge, et. al., "BPOG Response to Annex 2"

Christelle Simpson-Platre, et. al., "Retrospective evaluation of low pH viral inactivation and viral filtration data from multiple company collaboration"

New Trends Driving Prefilled Syringe Development

Rebecca Stauffer, PDA

The PDA Letter *interviewed Pfizer's* ***Mathias Romacker*** *at the 2015* Universe of Pre-filled Syringes and Injection Devices *conference in Vienna on what's next for prefilled syringes and devices. Romacker was a member of the planning committee for the first* Universe of Pre-filled Syringes *meeting in 2004.*

PDA Letter: Tell us more about your involvement in the prefilled space. I understand you were part of the team behind the first PDA *Universe of Prefilled Syringes* conference. Why was that the right time for PDA to have this meeting?

Romacker: In 2004, prefilled syringes were moving from small specific areas, such as anticovalents or vaccines, into other particular areas. You could really see the growth back then, albeit from a smaller base. It was becoming tremendous, reaching double digits year after year and we really felt that it would actually be a good thing to get all the stakeholders in this area together at a conference to exchange information and share some thoughts. We invited the syringe manufacturers and the rubber component suppliers. We invited the machine makers. We invited contract manufacturers. We invited a lot of different areas. Initially, it was very Eurocentric. But obviously when it moved to the U.S., it was equally as successful.

PDA Letter: Did you think it get as big as it has now with over 100 exhibitors and over 600 attendees each year?

Romacker: I'll give you an honest answer: No! When we approached PDA in 2004, we could not guarantee a certain [level] of attendance. But we talked to some people in the industry, like suppliers, and asked "What do you think of the idea?", and the response was extremely positive. So, we felt prefilled syringes are definitely going more mainstream…but if you consider we moved from a 100 people in 2004 in Hanover to 1,000 people in 11 years—that is a crazy growth rate for an industry that's very mature.

PDA Letter: So, what do you see as the larger trends right now in the prefilled syringe sector?

Romacker: When we started this conference, it was called the *Universe of Prefilled Syringes.* In 2007 or 2008, the name was changed to *Universe of Prefilled Syringes and Injection Devices.* And rightly so. But in 2006 when you look at, for example, disposable autoinjectors based on prefilled syringes, you have exactly two of these that were commercialized. Everything was still really in its infancy. This year we saw 16 or 17 autoinjectors being launched. For something that was really niche, it's now hitting the mainstream. Also, when you look at this exhibition here, [there are] over 100 exhibitors. You have now for each category of devices multiple offerings. Ten years ago, you just did not have that. In a certain way, I think even businesses, stakeholders—people realize a great opportunity. There is really a need here to really grow this.

A lot of the newer drugs are biologics, and these biologics are often needed for chronic lifelong [conditions]. And the nature of [these products] is that they need to be injected. So, now you have all those patients who have obviously been diagnosed and need a biologic for their therapy. Now they have to self-inject themselves. I think this industry is really helping tremendously to make that palatable to patients, so that they can actually accept a certain direction and also remain adherent.

PDA Letter: What's your take on the rise of "smart" health technologies?

Romacker: At this conference, I don't really see a lot of connectivity or smart device specialists. A lot of the established players realize there is an opportunity here to maybe partner with some of the players that previously didn't look at pharma. On the other hand, nobody quite knows what it means yet. Apps have [actually] been around for quite some time. It seems people don't use them. So, clearly, the challenge is how do you actually leverage that kind of technology—smart devices, connectivity, digital health, whatever you want to call it. I personally think the opportunity here is really that you need something more passive. Something that maybe builds on a combination product or device that then really communicates with something. But we still have to figure out who will be the stakeholders, what value does this bring to each of the different stakeholders, and how do you get this all together? Then, also who will actually be the players that will take this forward?

I'm very certain and bullish that in six to seven years we're going to see a lot of new [technology and applications] coming out. I think injectable drug delivery is here to stay, at least for the next 11 years, while of course talk about digital health and smart devices has just started to evolve.

[This interview reflects the views and opinions of Mathias Romacker in his personal capacity and does not reflect the views of Pfizer Inc. or any of its affiliates.]

About the Expert

Mathias Romacker is a Senior Director of Device Strategy/Marketing at Pfizer.

Yes, We Can Meet the Challenges of Innovation

Wenzel Novak, PhD, Groninger

The healthcare industry is changing, and there is increasing patient demand for self-medication options. The demand for more flexible and specific medications requires manufacturers to offer a variety of products. This not only means offering different formulations, but also adapting all downstream and upstream manufacturing processes around personalized products.

Industry experts foresee the following trends: complex and detailed molecules, reduced quantities per batch, increased sensitivity in current manufacturing processes, requests for modified containers—both in design and in material—optimized filling processes for shear forces and reduced loss of product. Additional administration and application modifications must be created to answer market trends in the near future.

Fortunately, there is no need to reinvent the wheel, as the industry often has solutions in the market. For example, certain polymers, coatings, new materials and container designs, as well as disposable systems for downstream and upstream manufacturing are all presented as standard offers in manufacturing. Disposable filling systems combine traditional knowledge and modern thinking. Equipment can be changed in just two hours to run a different product that also includes the decontamination cycle.

With all of these points in mind, creating a knowledge base to choose the best solutions remains a challenge. Along with product needs and patient risk/acceptance, economical aspects must also be considered. This begs the question, how can this comprehensive information be gathered? One option involves listening to industry experts, futurists

Continued at bottom of page 21

How Does Microbial Control Impact Patient Safety?

Renee Blosser, U.S. FDA

Regulation of parenteral products and an understanding of risk assessments associated with the manufacturing of sterile injectable products are critical components to ensuring patient safety. The U.S. FDA has long emphasized the need for microbial control in pharmaceuticals and biologics. For example, in 2011, FDA staff published an article in *American Pharmaceutical Review* ***(1)*** that addressed the complexities of biologic product manufacturing and the impact of microbial contamination on the finished drug product, company finances and the potential for drug shortages. The authors also presented case studies focusing on identification of microbial contaminants and investigations into the root cause of the contamination, and discussed the importance of reviewing data for microbial trends on a regular basis.

A successful risk assessment will evaluate a variety of elements, including facilities, equipment, personnel, raw materials, manufacturing processes, and quality systems to determine their collective impact on microbial control. FDA investigators routinely examine these interdependent elements during inspections to determine if the overall process operates in a state of control to produce a safe and effective finished drug product.

PDA 's *11th Annual Global Conference on Pharmaceutical Microbiology* will help answer questions you might have related to these challenges in microbial control and will explore microbiologists' role in ensuring the quality of parenteral products.

Other scientific presentations will explore innovative technologies, workforce development, and a variety of other topics that highlight the critical role pharmaceutical microbiology plays in promoting public health. Other popular sessions will return with new presentations, including the ever-popular "Emerging Leaders" and "USP Updates." The final day of the conference will focus on standards and regulation, including an "Ask the Experts" panel discussion that gives attendees an opportunity to pose questions directly to FDA and industry personnel with expertise in manufacturing and regulatory issues.

Yes, We Can Meet the Challenges of Innovation continued from page 20

and creative minds. The *2016 PDA Universe of Pre-filled Syringes and Injection Devices* will once again offer a forum to develop a knowledge base. Regulators, pharmacists, quality-focused manufacturers and suppliers will discuss the traditional and modern aspects of our industry. State-of-the-art approaches will not only be reflected in case studies, but will also open minds to new, effective ideas in the near future—connecting people today to create better solutions for tomorrow.

2016 PDA Universe of Pre-filled Syringes and Injection Devices and PDA Education courses

Huntington Beach, Calif.
Oct. 17–21
www.pda.org/2016prefilled

Reference

1. Suvarna, K., Lolas, A., Hughes, P. and Friedman, R. "Case Studies of Microbial Contamination in Biologic Product Manufacturing." *American Pharmaceutical Review* 14 (2011) 50-56.

11th Annual PDA Global Conference on Pharmaceutical Microbiology and PDA Education courses

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www.pda.org/2016micro

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- Establishing QTPP for Biosimilars (Case Studies)
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Immediately following the Conference, on June 22, PDA's Education Department will host two courses as part of the *2016 Biosimilars Course Series*. These courses will help you understand the challenges that must be considered before entering the field of biosimilar manufacturing.

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Combination Products Continue to be Key to Biologic Therapies

Ronald Iacocca, PhD, Eli Lilly and Company

The introduction of biologic therapeutics has led to a rapid expansion in the use of combination products. These life-changing medications greatly enhance the patient experience when used in conjunction with a device that enables easier dosing. This results in greatly improved medical outcomes due to better patient compliance. In today's complex regulatory space, how does one design a patient-centric product with connectivity to electronic devices, while also meeting all of the quality, safety and medical requirements?

One of the challenges encountered with combination products is the development of appropriate human factor studies that are patient-centric while still delivering the desired dose. Consider patients with rheumatoid arthritis. This illness can significantly reduce manual dexterity, so developers need to take this into account when developing a drug product. Such human factors considerations must be included in the device design and in the methods that assess the mechanical functionality of the device. Companies marketing combination products need to ensure that there is a clear line of site between the design, testing and human interaction. These methods must then be incorporated into the development of release and stability testing to ensure the combination product works properly for its intended lifetime.

The *2016 PDA Drug Delivery Combination Products Workshop* will pull together experts from key areas of drug delivery development and manufacturing to speak on this topic as well as others. Because of the U.S. FDA's participation in the meeting, attendees will have a first-hand opportunity to ask questions about current regulations for combination devices.

This workshop is appropriate for anyone working in the field of combination products, and the program planning committee invites anyone invovled in these areas to attend the workshop in October.

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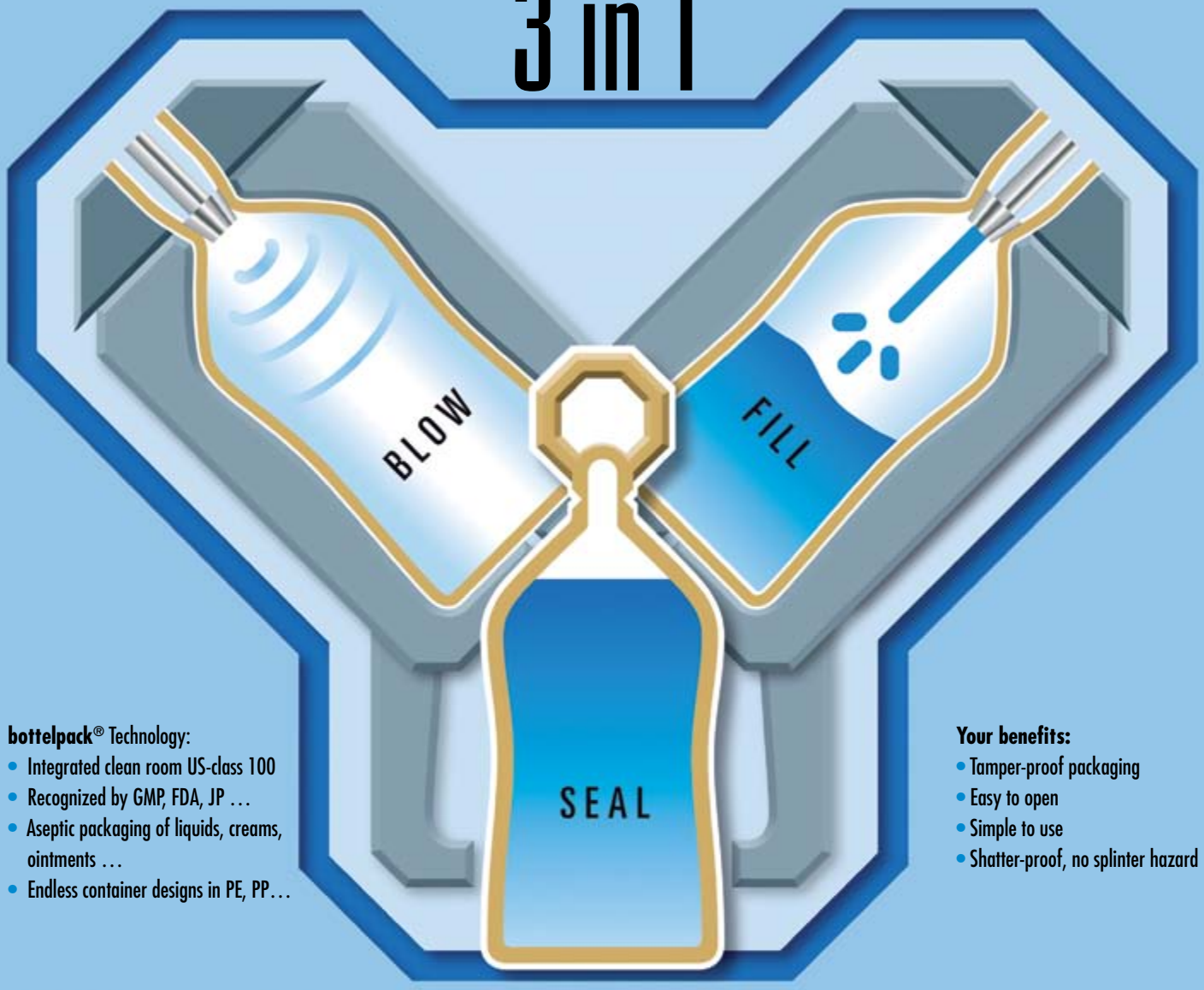

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17-18

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Tokyo, Japan
pda.org/PFSSeminar

18

2016 PDA Visual Inspection Interest Group Workshop
Bethesda, MD
pda.org/2016VisualWorkshop

24-26

GSA Schedule Contract GS-02F-113BA

Management of Aseptic Processing
Bethesda, MD
pda.org/2016ManageAP

31-1

BERLIN – 2016 PDA Workshop: Current Challenges in Aseptic Processing, Potential Changes in EMA/PIC/S Annex 1 Revision
Berlin, Germany
pda.org/2016AnnexBerlin

JUNE

1

PDA Metro Chapter Microbial Monitoring Day
Somerset, NJ
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6

Viral Safety of ATMPs
Berlin, Germany
pda.org/Viral2016

6-10

GSA Schedule Contract GS-02F-113BA

Aseptic Processing Training Program – Session 3 SOLD OUT
Week 2: June 27 – July 1
Bethesda, MD
pda.org/2016Aseptic3

7-8

Advanced Therapy Medicinal Products
Berlin, Germany
pda.org/EU/ATMPs2016

9

Practical Application of GMP for Development of ATMPs
Berlin, Germany
pda.org/EU/TCATMPs2016

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GSA Schedule Contract GS-02F-113BA

Fundamentals of Cleaning and Disinfectant Programs For Aseptic Manufacturing Facilities
Bethesda, MD
pda.org/2016Clean

20-21

2016 PDA Biosimilars Conference
Baltimore, MD
pda.org/2016Bio

21-23

GSA Schedule Contract GS-02F-113BA

Validation of Biotechnology-Related Cleaning Process
Bethesda, MD
pda.org/2016Biotech

22

2016 Biosimilars Course Series
Baltimore, MD
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28-29

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30

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30

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pda.org/EU/GMPforAPIs2016

30

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pda.org/EU/Cleaning2016

30 – 1

Root Cause Investigation
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30 – 1

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Big Data Meets Vaccine Manufacturing

A Manufacturer Discovers What Happens When You Look at the Data

Rebecca Stauffer, PDA

Since the late 2000s, "Big Data" has become a buzzword used throughout various industries. The term itself refers to datasets "so large and complex that they become awkward to work with using standard statistical software" ***(1).*** Big Data is about more than just the collection of data. It's about using it to make decisions based on efficient analysis. Making sense of it is the challenge facing most companies. But companies are solving this challenge and taking specific actions based upon the information gained. For example, Netflix used data about its subscribers to determine what they want to see "before they do." This prompted the television and movie streaming service to develop its popular series *House of Cards* and *Arrested Development* ***(2).*** Other uses of Big Data include optimizing the workforce, improving financial performance, selling intelligently, minimizing equipment and asset failures, and leveraging customer value ***(3).*** For pharma, efforts to harness Big Data have primarily been focused on clinical applications. Bristol-Myers Squibb turned to Big Data to reduce the time it took to run simulations of clinical trials ***(3).***

But what about manufacturing? How can this segment of the industry create its own Big Data success story?

Merck's CIO of Manufacturing, **Michele D'Alessandro,** offered a case study at the *2015 PDA/FDA Vaccines Conference* ***(4)*** to show how manufacturers could potentially increase vaccine yield using Big Data analytics. In 2014, her team led a six-month project at Merck to analyze the root causes of variations for the company's two plants that manufacture its Gardasil® vaccine product.

"The Gardasil vaccine facilities, which this case study applies [to], are highly automated," said D'Alessandro. "There are hundreds of process parameters that are routinely acquired and archived electronically. That's a good thing for us for this case study. But there are also a number of process parameters that are still recorded manually…part of the effort around this case study was to also look at this data."

Of all the aspects of production the team could analyze, they targeted process variability.

"I think that all would recognize that production processes in this case are inherently variable," she said.

Given the high level of automation and data collected and the variability of the processes, the team's goal was to reduce variations and increase process robustness, and ultimately, improve process yield.

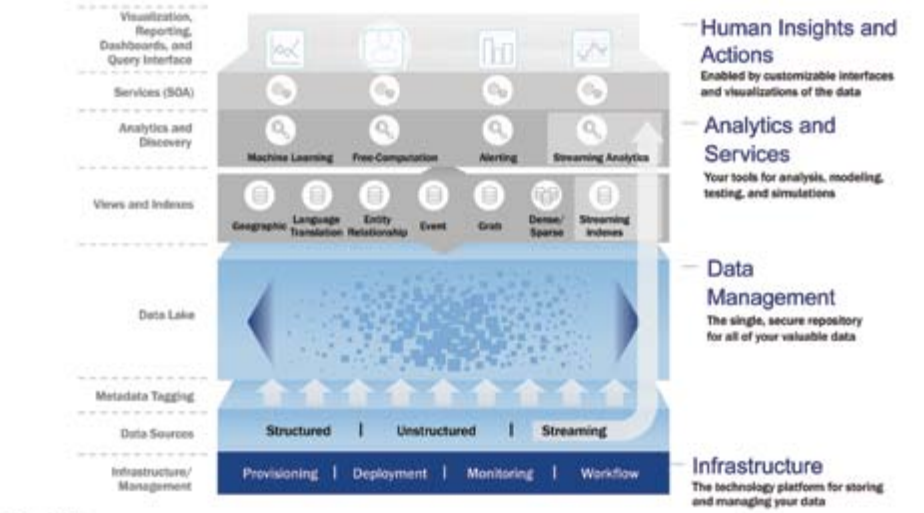
"And so that began a six-month journey in 2014," said D'Alessandro.

The team reviewed data for batches collected over five years. The company already had experience using Big Data for inventory management, transportation optimization and more traditional business/financial applications, but this would be the first foray into manufacturing.

The team used a "novel" approach that relied on a "modern data science platform," she said. "We do have classic data warehouse platforms at Merck, but that's not what we utilized for this case study, and that is what made this experience very unique for us."

The platform is a Hadoop architectural environment which Merck had already used for business process improvements. "This was the first time we brought it into manufacturing operations, and it was important for us to leverage this platform because it is a Big Data platform which means it handles large amounts of data."

Figure 1 Conceptual Architecture



Hadoop is a Java-based open source framework for distributed storage and processing of very large datasets. It was developed by Apache and initially released in 2006 ***(5).***

New technologies like Hadoop made the case study possible. "The reasons why Hadoop is so valuable is the amount or size of the data that you can process and the speed to which you can do it. The second is it allows us to combine data from a variety of different sources in real time."

Using the system, Merck pulled in data from a variety of systems, including process data historians, change control systems, LIMS, Manufacturing Execution Systems, process control systems and the manual data that were recorded.

The ability of the Big Data platform to handle large datasets **(Figure 1)** was critical since the project entailed analyzing five terabytes of manufacturing data (equal to 5,000 gigabytes) from all aspects of vaccine production—fermentation, purification and media prep.

"We made more than 5,500,000 batch-to-batch comparisons to look for process similarities and differences, and tie those into aspects of yield," said D'Alessandro. We had over 1 bil. records to process.... We wanted to rapidly look at data, put it in front of subject matter experts, get recommendations, and implement changes to models, and then turn them around again."

Within 7–10 business days, the team was bringing data in and computing it. "So if your data hold took anywhere longer than a day, you couldn't have that day. We set some pretty aggressive targets with the speed in which we wanted to learn from it."

Stringing Together Strands of Data

With the Big Data tools, the team was able to combine various types of data together that had not been brought together before. "Think of this as highly structured data and highly unstructured data being brought together for analysis and aggregation," said D'Alessandro.

"The beauty of this environment is that we can bring all that data together and we can analyze both the size and the scale and the complexity of that information in one environment."

Article at a Glance

- Pharma companies can harness Big Data for more than marketing and clinical research
- Company used Big Data as part of a pilot to analyze vaccine yield
- A definite need exists for data scientists in this area

The team used a "novel" approach that relied on a "modern data science platform"

Technically, the team was challenged to analyze disparate batch data.

"The other thing that I would share that was really a technical challenge since I made much of the technology sound easy, is that we had to marry together significant batch data, and many of our batch series data were not like in kind. There might have been characteristics about some batches that were different than others; they might have had different timescales to them. And we were challenged from a technology perspective to combine all this data together for meaningful insight."

To do so, the team used a time series method known as Dynamic Time Warping. "It sounds pretty fancy," she said. "What it really comes down to is a database with software tools on top of the database that calculate similarities and differences between time series data, and in this case, batch data, that allow us to understand the similarities."

Challenges Met, Lessons Learned

"Not unlike many of our projects that are experimental in nature, we took in a number of learnings and challenges—technology not being the majority of it," said D'Alessandro.

"First and foremost, we had challenges around people, in particular, knowledgeable subject matter experts and data scientists that we could rely on." At times, the team "had to go external to get the right competency and skillset."

The team also faced challenges collecting the process data. "Collecting the data from five years was great, but in some cases people didn't expect that they'd ever use it, so there were times when the data might have been incomplete, and we had to go back and try and figure out pieces of missing data."

Learnings Applied to Operations

Based on the data analyses, the team found "really interesting linkages between properties and fermentation" that influenced yield in purification, which helped explain yield in the final product.

In addition, the team learned how to use the analytical tools and the manufacturing and process data to analyze problems like variability, and "more importantly," to identify leading indicators around variability before they actually manifest themselves in a problem. "So that was probably the most noteworthy part of the outcome," stated D'Alessandro.

Another "major" learning was that the company has to "treat data as an asset and as a resource and to put the right amount of stewardship around it."

D'Alessandro is encouraged by the project and considers her team's work as indicative of the future convergence of Big Data and pharma manufacturing, and even the vaccine industry.

"What's exciting for us is that we've actually taken the benefits you've seen in this case study and have made them part of an ongoing capability that's now integral to Merck. Since [this] work, we've already applied this type of technology, this architecture, and this framework, to other specific process robustness issues...but the most rewarding part for me is that nearly a year later, we've made this a competency within our manufacturing environment."

[Editor's Note: The *PDA Letter* interviewed Michele D'Alessandro for a three-part "On the Issue" video series available here: https://www.pda.org/pda-letter-portal/multimedia/video]

References

1. Snijders, C., Matzat, U., and Reips, U.D. "'Big Data': Big Gaps of Knowledge in the Field of Internet Science." *International Journal of Internet Science* 7 (2012): 1-5. http://www.ijis.net/ijis7_1/ijis7_1_editorial.pdf
2. Carr, D. "Giving Viewers What They Want." The Media Equation. *The New York Times,* Feb. 25, 2013, B1 http://www.nytimes.com/2013/02/25/business/media/for-house-of-cards-using-big-data-to-guarantee-its-popularity.html
3. Morgan, L. "Big Data: 6 Real-Life Business Cases." *InformationWeek,* May 27, 2015 http://www.informationweek.com/software/enterprise-applications/big-data-6-real-life-business-cases/d/d-id/1320590
4. D'Alessandro, M. "Case Study: Using Information Technology-Based Tools to Optimize Yields in Vaccine Production." Presented at the 2015 PDA/FDA Vaccines Conference, Dec. 2, 2015, Bethesda, MD.
5. "What is the Hadoop Distributed File System (HDFS)?" *IBM.* IBM.com. Accessed March 29, 2016. http://www-01.ibm.com/software/data/infosphere/hadoop/hdfs/

About the Expert

Michele D'Alessandro is Vice President and CIO for the Manufacturing Division with Merck & Co., Inc. In this role, she provides strategic leadership, oversight and delivery of information technology and digital solutions for the Merck Manufacturing Division.

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The Dangers of Underestimating Method Variability

Nanda Subbarao, Biologics Consulting

[Editor's Note: The author covered the topic of analytical methods for vaccines at the *2015 PDA/FDA Vaccines Conference*.]

As a consultant, I have personally observed how method variability is often underestimated in pharmaceutical laboratories. This can lead to misinterpretations of data presented in the CMC documentation. Such underestimations of variability should not occur in laboratories with robust overarching quality systems that cover all facets of a pharmaceutical laboratory's operations. Yet, in practice, I have seen quality systems breakdown for various reasons during routine laboratory operations, mostly due to limitations of time and resources.

Below are a few of my observations from conducting laboratory audits and CMC reviews, including some specific reasons why laboratory systems break down. The results can have severe repercussions such as failed pivotal stability studies or batches that fail product release specifications. An awareness of some of these factors could perhaps help prevent them in the future.

In my experience, the most common root cause of underestimated method variability in the industry is inadequate time for method development and validation. Project deadlines can force compression of method development time to unrealistic levels. Picture this scenario: a laboratory can only perform a couple of successful runs before rushing into the method validation stage. No time is set aside for method optimization before validation begins. Aware that the method is not well-developed, laboratory personnel set the widest possible validation acceptance criteria, barely supporting the product specification. When the validation results only marginally meet the already wide acceptance criteria, the laboratory has no time to optimize the method and repeat the validation. This often results in unrealistic timelines as the root cause for laboratories justifying acceptance of unsatisfactory methods that do not adequately support the product specification.

Another example I've encountered of underestimated method variability is related to documentation protocol. To save time, occasionally sponsors do not provide a well thought-out method validation protocol. The justification given for this is based on the belief that the U.S. FDA does not require a copy of the Method Validation Protocol in the CMC section of the application. Without the method validation protocol with its procedures and preset acceptance criteria, such companies have a tendency to justify that the method is acceptable, even when the precision evaluated during method validation is not adequate to support the product specification. The July 2015 FDA guidance ***(1)*** should ultimately be a deterrent for such practices.

On the topic of FDA guidances, the 2006 guidance on out-of-specification (OOS) test results ***(2)*** does not explicitly mention the words "method validation data" in the section where it discusses the guidance's scope. Sponsors have pointed to this when explaining to me why they believe that the OOS guidance does not apply when failure is encountered during method validation exercises. I also see cases where the laboratory simply ignores data from any runs where system suitability fails. It is true that such events should not occur in laboratories with robust quality systems. Such systems, however, buckle under the twin pressures of deadlines and limited resources, as my experience has shown.

Full Understanding of Methods Needed

Another cause of underestimated method precision is the practice of evaluating precision of only the last step of the SOP during method validation. In the CMC documents and method validation packages that I review, I often see cases where a single aliquot of the sample is extracted and three dilutions of that single extract are injected on the HPLC. Such a procedure in effect ignores the variability introduced by the extraction step, which is likely to contribute most to the method variability. I have even seen cases where the reported RSD of the chromatography method is calculated from three injections of a single final dilution of the sample extract. In effect, the calculated RSD of the triplicate injections ignores all but the variability of the HPLC instrument. ➤

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I have seen similar problems in the validation of ELISA-based methods. For example, three aliquots of the cell-free medium prepared from one batch of the product were tested on an ELISA plate to determine the level of residual trypsin in a cell therapy product. The method validation protocol in effect ignored the method variability introduced at the step where the cell-free medium is prepared, i.e., the step likely to introduce the highest variability to the overall assay. Such mistakes during method validation probably originate because the method of validation is not fully understood.

Method variability is often higher than that reported in method validation reports because method validation in QC laboratories is generally performed by the most proficient analysts in the laboratory. The precision reported in method validation reports will therefore be lower than the precision in the hands of an average QC analyst. The problem is further exacerbated if the training for the QC analyst is abbreviated due to tight timelines. In addition, sample throughput rates increase after implementation in the QC laboratory leading to subtle changes in the method, which could impact method precision.

Unsatisfactory method transfer procedures and practices can also result in underestimation of method precision in the QC laboratory. In particular, intensive steps that are performed manually are not updated when transferred from the sending laboratory to the receiving laboratory. The relatively brief method transfer exercises can be inadequate for the receiving laboratory's personnel to become familiar with the method. The implemented methods in the QC laboratory could, therefore, have a higher variability than that reported in the method validation package.

Lack of revalidation or reevaluation of methods when product quality "creeps" over time is another cause of unexpectedly high variability. The reagents and key supplies such as chromatographic columns can also change gradually over time. The impact of such changes becomes visible, particularly in situations where there is a long time-gap between test points (e.g., after the second year of stability studies). Changes in laboratory personnel and insufficient training on the method also occur frequently when time points between testing extend out. Lack of expertise in the method and data trending, I believe, is probably the root cause of such occurrences.

Increased variability can also occur because of changes in laboratory conditions. I have seen a case where the variability of an HPLC method increased during weekends, particularly during winter. Upon investigation, the root cause was found to be the drop in room temperature during weekends, which in turn was caused by the site's new energy saving policy. The RSD of the chromatography method was known to be temperature sensitive and therefore the impact of lowered laboratory temperature was explained.

One option for controlling all the factors impacting method variability is to implement a QbD-type approach so that the QC laboratory can adhere to a well-defined design space over the lifecycle of the product. The quality of the data will improve by spending the available resources early in the development project, and the "right first time" approach leads to significant savings over the life of the product. However, as we have learned, this approach takes commitment and resources that may not always be available at the time it is needed. Pharma companies must often find the right balance of project risk, cost and regulatory compliance appropriate for the product and the stage of development, as discussed by **Pierre Doutte** and **Pascal Bolon** in a 2013 *BioPharm International* article ***(3).*** The lack of venture capital can force companies to adopt a relatively shortsighted approach to method development-related activities. This is particularly true in companies whose business model is to sell or license the product after some initial development stage. The value of such a product may not hinge on a well-developed CMC section.

In summary, over the years I have seen many ways in which underestimation of method variability occurs in pharmaceutical laboratories. Well thought-out method validation protocols can help evaluate the variability correctly. In addition, robust method transfer exercises and lifecycle management are required to maintain the method performance at the level observed during the method validation exercises. It is important for sponsors to provide methods that are backed by a robust method validation package to appropriately face the challenges of managing a product over its lifecycle. The regulatory need for a good method validation package in the CMC section of the application is only secondary to the business need for reliable methods.

References

1. Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics, U.S. FDA, July 2015 http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm386366.pdf
2. Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, U.S. FDA, October 2006 http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070287.pdf
3. Douette, P., and Bolon, P. "Analytical Method Lifecycle: A Roadmap for Biopharmaceutical Development." *BioPharm International* 26 (2013). http://www.biopharminternational.com/analytical-method-lifecycle-roadmap-biopharmaceutical-development

About the Author

Nanda Subbarao is currently a Senior Consultant with the Biologics Consulting Group specializing in analytical, stability, CMC and GLP/GMP quality systems.

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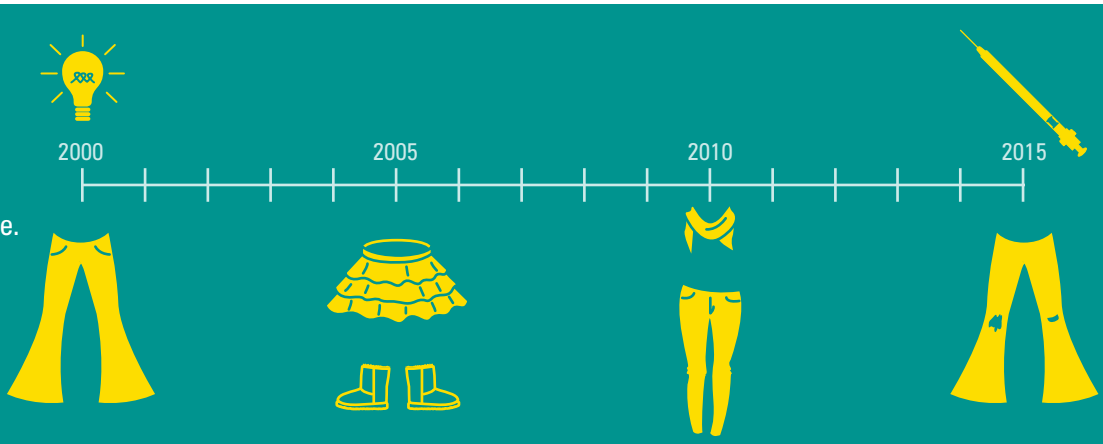
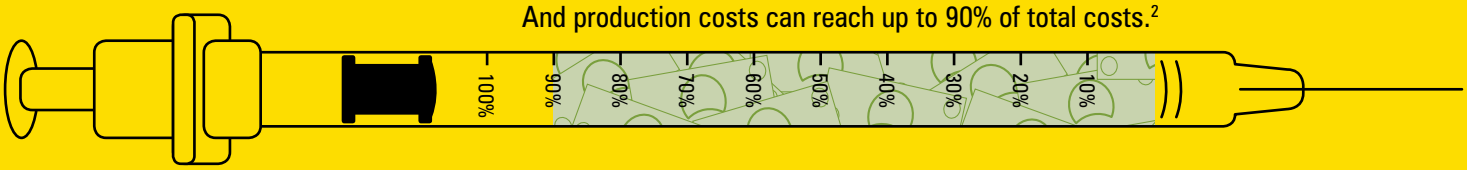
The Economics of Vaccines

It can take 15 years or more to develop a vaccine and cost between $163 and 518 million (USD), according to the WHO.[1] That's about the average cycle length between bellbottoms coming back in style.

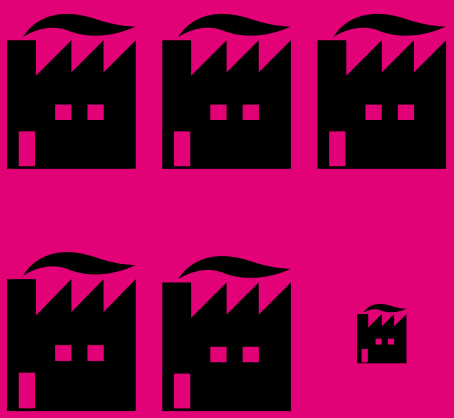


And production costs can reach up to 90% of total costs.[2]

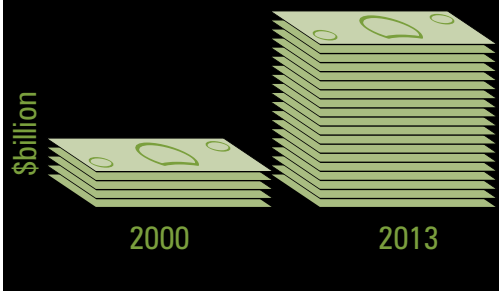


Vaccines only account for 2–3% of the entire pharmaceutical market.[3]

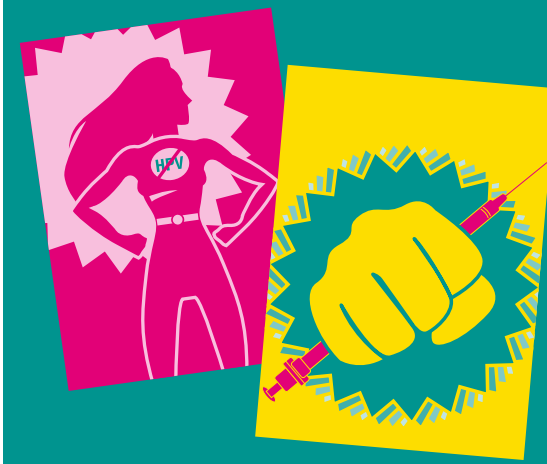
5 manufacturers produce the majority of vaccines.[4] GlaxoSmithKline, Merck, Sanofi Pasteur, Pfizer, Sanofi Pasteur MSD



The vaccines market share has increased from $5 billion in 2000 to $24 billion in 2013.[3]



In the early 2000s, two new vaccines, one for pneumococcal meningitis and another for human papillomavirus, proved to be blockbuster products.[5]



Sources

1. Abraham, A. "Risk based approaches to monitoring of vaccine clinical trials." tinyurl.com/hornqmz
2. "Key Concepts: Economics of Vaccine Production." tinyurl.com/zsa9nen
3. Kaddar, M. "Global Vaccine Market Features and Trends." tinyurl.com/h9o7oxc
4. "Vaccine development and implementation." tinyurl.com/gtortq6
5. Lam, B. "Vaccines Are Profitable, So What?" tinyurl.com/nhwk98y

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The Impact of FDA's eCTD Guide on Combo Product Submissions

Bonnie I. Scott and James A. Boiani, Epstein Becker & Green

In October 2015, the U.S. FDA issued the Electronic Common Technical Document (eCTD) Technical Conformance Guide ***(1).*** This Guide, which supplements FDA's eCTD Guidance ***(2),*** provides sponsors with technical recommendations regarding the electronic submission format for INDs, NDAs, ANDAs, certain BLAs and master files submitted to CDER or CBER.

For sponsors submitting applications for combination products, the Guide has some favorable aspects, but it also creates important concerns. On the one hand, it reflects FDA's effort to clarify its expectations regarding combination product submissions. In addition, the recommendation that sponsors include a "roadmap" that references where information is located within their applications is useful since it facilitates FDA's review and allows sponsors flexibility in organizing their applications. On the other hand, concerns surrounding certain Guide recommendations with respect to combination products are significant, as reflected in multiple comments that FDA received from industry.

These key concerns primarily focus on the following two specific recommendations in the Guide:

- Placement of device and combination product-related information and human factors testing data in different sections of the application than sponsors typically use

- Inclusion of documents demonstrating compliance with device and combination product cGMP requirements (set forth in 21 CFR Part 820 and Part 4, respectively).

Regarding the first concern, the Guide recommends placing the device and combination product information in section 3.2.P.7 of the application. Yet, historically, sponsors have placed this information in section 3.2.R, a practice previously accepted by FDA and currently accepted by other world markets. As a result, sponsors may need to develop very different sections for the United States than for other regions—a significant administrative burden. Further, varying application structures for the same product could lead to problems down the line as sponsors would have to manage supplements, annual reports and other submissions made throughout a product's lifecycle.

Another concern comes from the Guide's recommendation to place human factors testing data in Module 5 (clinical study reports section) rather than Module 3 (quality section), which is where sponsors have historically included this data. Although human subjects participate in human factors testing, these are often simulated use studies (i.e., design validation). These have historically *not* been considered "clinical studies." This has led to a concern among innovators that placing human factors data in Module 5 indicates that these studies are now considered "clinical studies," and therefore, subjects applicants to prescription drug user fee requirements. Although inclusion in Section 5 does not automatically trigger user fees, innovators are concerned that this could be a signal of user fee changes to come.

Another concern is that FDA is signaling that future device changes made and validated using a human factors study could require submission of a more onerous Prior Approval Supplement (usually required for submissions with "clinical studies"), when they previously may have only required a Changes Being Effected ("CBE") or Changes Being Effected in 30 days ("CBE-30") supplement.

PDA Task Force Seeks Clarification

With regards to the second key concern, the Guide's recommendation that sponsors provide information "to demonstrate compliance" with device and combination product GMP requirements is not consistent with statute, FDA regulations, and prior Agency policy statements. Requiring submission of this information could also create major administrative challenges for sponsors who would need to make filings each time there is a GMP-related change to keep applications current. This would put a heavy burden on pursuing incremental improvements in manufacturing that benefit patients. There is hope that this is not the intent of FDA, and that FDA only plans to continue requesting basic manufacturing party information to support planning for preapproval inspections (a longstanding practice). But if so, the meaning of the Guide will need to be clarified, or its words may be misinterpreted both outside and inside the Agency.

Besides these specific concerns with the Guide as discussed above, it is unclear whether the Guide could, at this point, be strictly interpreted by FDA and referenced in "refuse to file" decisions. Although the document states that "when *finalized*, [the document] will represent the current thinking of [FDA] on this topic" (emphasis added) the Guide is not specifically titled as "Draft" ***(1).*** This adds another layer of uncertainty for combination product sponsors. Will FDA divisions begin implementing the Guide before comments are considered and revisions made to the document? Hopefully not, but at this time, it is not entirely clear this won't happen.

A PDA task force submitted a response that included these points in January 2016. In reviewing these comments, this group hopes that FDA will give additional consideration to the practical impact of its recommendations on the combination product industry and make changes that facilitate submission of applications for new and innovative combination product technologies in the United States.

Members of the commenting task force were **Lee Leichter** (lead), P/L Biomedical; **Tim Chesworth,** AstraZeneca; **John Finkbohner,** MedImmune; **Douglass Mead,** Janssen; **James Boiani,** Epstein Becker & Green; **Jennifer Hefele,** Pfizer; and **Suzette Roan,** Biogen. A copy of the PDA response is available on the PDA website: www.pda.org/scientific-and-regulatory-affairs/regulatory-resources/pda-regulatory-commenting/2016-pda-regulatory-comments.

References

1. eCTD Technical Conformance Guide, U.S. Food and Drug Administration, Oct. 2015 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf
2. Guidance for Industry: Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, U.S. Food and Drug Administration, May 2015 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf

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Future of Research, Future of FDA Tied Together

Monica Caphart, U.S. FDA, and Susan Schniepp, Regulatory Compliance Associates

How can organizations and companies working on solutions to rare diseases and disorders drive effective research? And what is the U.S. FDA doing to support development of drug products in this space?

Research is critical to advancing healthcare and developing the next generation of drug products. Medical doctor **David Fajgenbaum** found himself plunging into the depths of Castleman's disease research after the rare autoimmune disease nearly killed him. This led him to co-found the Castleman Disease Collaborative Network. During his research, Fajgenbaum discovered researchers were working in silos, driven by misaligned incentives.

At the *2016 PDA/FDA Joint Regulatory Conference*, hear how Fajgenbaum's organization approached these issues in his keynote address. He will discuss the progress his organization has made in the short time it has been in existence, and how it can serve as a model for other groups looking to accelerate research on rare diseases. In addition, you will hear FDA discuss efforts on curing disease from the many perspectives and on the future of drug safety.

Additionally, the theme of this year's conference is "Aligning Manufacturing Goals with Patient Needs through Successful Innovation and Compliance," and marks the 25th year of collaboration between FDA and PDA. Most sessions will provide a retrospective of the last 25 years, highlighting specific issues so participants can see how far manufacturing and regulation have come in the pharmaceutical industry and where we need to go in the future.

The conference this year offers five plenary sessions covering a variety of topics, including compliance—a key issue. The third plenary will offer insight into the question of compliance versus product quality, including the many approaches to compliance and will contrast the "checklist" mindset compared to a more proactive and preventive approach.

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One Coin, One Relationship When it Comes to Outsourcing

Steve Falcone, Amgen

Is your company effectively using outsourcing as part of its overall manufacturing or testing strategy to bring therapies to market? Or is your company the one providing these solutions to an ever wider range of customer needs, while also keeping pace with new expectations in the evolving regulatory environment? Every coin has two sides, but there is still only one coin, and that is what is important to remember in the outsourcing relationship; while it has two sides, there is still only one relationship. Through collaboration and effective communication, great results can be achieved through effective outsourcing by both sides supporting this important partnership.

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Whether a large company needs to manufacture a new autologous therapy or a small company needs testing on preclinical material, there must be an awareness of the obstacles that the outsourcing partner is juggling. The interface of customers' quality system needs along with the advancement of new expectations from regulators, such as quality metrics, gives a company important insight into supporting an effective partnership.

More often than not, company culture becomes a key area inadvertently managed through the quality agreement. This is why the due diligence evaluation should include some consideration on these so-called "soft issues" in advance, so there are no surprises on how to resolve issues, or even a need to debate on what exactly is an "issue." Good planning and anticipation will support a relationship poised for success but able to cope with the unforeseen challenges.

At the *2016 PDA Outsourcing/CMO Conference*, you will hear from both sides of this relationship on what is needed for effective collaboration and what it takes to make the relationship succeed in a diverse and evolving regulatory environment. I encourage you to attend this important conference as a means to help advance your organization's objectives with the knowledge of effective outsourcing.

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Reducing Analytical Method Steps for Accelerated Product

Stephan O. Krause, PhD, AstraZeneca Biologics

With an increasing number of products being considered for accelerated development, both the industry and regulators are looking for ways to safely hasten product development and approval times to ensure availability of innovative and low-cost drugs for patients. The development and validation of test methods during the regular product development lifecycle is a challenge. Not surprisingly, an accelerated timeline magnifies this challenge. Many developers struggle with bridging early-stage, fit-for-use test methods with the validated late-stage methods needed for process performance qualification (PPQ)/validation, routine production and post-approval requirements ***(1).***

For biosimilars, the rigor of method development, qualification, and/or validation for specific quality attributes needs to be commensurate with their impact on analytical similarity demonstrated between the biosimilar and reference product, and consideration should be given to the potential for delays in product development and/or approval. Risk-based, practical concepts for how and when analytical methods are qualified, transferred and validated should be used and supported by industry and regulatory agencies. The method type, intended use (Tier 1, 2, or 3 quality attributes), and/or prior experience (e.g., analytical platform technology) should also be considered.

When demonstrating analytical similarity between the biosimilar product and the reference product, a grouping of the critical quality attributes (CQA) into three main risk categories is performed according to their criticality. Following a risk ranking for quality attributes, the CQAs are then grouped into Tier 1-3 categories (Tier 1 is the highest risk group) based on their potential impact on activity, PK/PD, safety, and/or immunogenicity ***(2).*** For example, the mode of action is typically a Tier 1 CQA and equivalence testing is, therefore, expected. **Table 1** lists the expected study model for each of the three criticality (Tier 1-3) levels.

Recently, an industry survey evaluated how manufacturers transfer analytical methods for biological drugs. Significant variations were observed among the surveyed manufacturers, specifically in the use of analytical method transfer (AMT) models, sample size, and setting of acceptance criteria ***(3).*** These results indicate that more pragmatic guidance is needed across the globe to support accelerated product development, such as pathways for biosimilars.

Industry Makes Case to FDA

Last September, the author presented an industry perspective on how to reduce analytical CMC steps in support of accelerated biological product development to CDER representatives at the U.S. FDA headquarters ***(4).*** This presentation followed up on a 2012 presentation delivered at CDER of the draft content from PDA *Technical Report No. 57: Analytical Method Validation and Transfer for Biotechnology Products* ***(5).***

At the most recent meeting, strategies for the analytical method lifecycle steps were discussed along with how they may minimize the risk of potential product development and approval delays. The suggestion to use analytical platform technology (APT) methods, and with it, the benefit of executing lower-risk, reduced method validation studies, was well received by CDER. An APT method is an analytical method used for multiple products and/or types of sample matrix without modification of the procedure. Similar to compendial methods, an APT method may not require full validation for each new product or sample type ***(3).*** A test method becomes an "approved" method when included in a marketing license application, and the license is approved.

Many Benefits to APT Methods

Additionally, the author emphasized further advantages of APT methods to the CDER representatives, highlighted here:

- APT status can be extended to additional products if the test method remains essentially unchanged through proper use of change control
- Similar to compendial method verification, "approved" test methods then can be verified (versus validated) for use of additional products
- Reduced method qualification and transfer studies could then be executed, provided the same sending and receiving units are used
- For additional product license applications, the sponsor should resubmit the initial method validation study report together with product-specific verification results (and reports)

Table 1 Tier 1-3 Quality Attributes for Biosimilars ***(2)***

Criticality Level (Tier 1 = Highest Risk)	Analytical Similarity Testing Model (Biosimilar vs Reference Product)	Acceptance Criteria
Tier 1	Equivalence Testing	Two-sided confidence interval of the mean difference is within $(-\delta, \delta)$.
Tier 2	Quality Range(s)	BP mean +/- X σ, where X should be appropriately justified
Tier 3	Raw data/graphical comparisons	Raw data and/or graphical (overlaid) results should "match"

- For bioassays, product specifications such as 50–150% should be tightened as early as possible, as FDA has significant concerns with regard to the mode of action potency assays. Conversely, there are less concerns for APT methods, such as typical separation tests, e.g., HPLC Size Exclusion

- For separation tests, an actual manufacturing batch should be used for test system control as test result drift and/or variation could be observed over time; degraded batch samples closer to the out-of-specification (OOS) level could provide better system suitability control, and they may also provide more confidence in the test results when results are close to the OOS level

A more in-depth review article will be published by the author in the *PDA Journal of Pharmaceutical Science and Technology.* Undoubtedly, there is still space to widen the field of low-risk options for the execution of method qualification, transfer and validation that would receive regulatory approval. Leveraging prior experience is essential for success in accelerated product development.

References

1. Mire-Sluis, A. et al., "Accelerated Product Development: Leveraging Industry and Regulator Knowledge to Bring Products to Patients Quickly." *BioProcess International* 12 (2014) tinyurl.com/zx7o444
2. Chow, SC, "On Assessment of Analytical Similarity in Biosimilar Studies." *Drug Des* 3:e124.
3. Krause , S. "Survey Results of Analytical Method Transfer Conditions Used by Global Biologics Manufacturers." *BioPharm International* 28 (2015): 22-30 tinyurl.com/j9aqy4o
4. Krause, S. "Specifications and Analytical Method Lifecycle for Accelerated Biologics." Presented at FDA headquarters. September 28, 2015.
5. Krause, S. et al., *PDA Technical Report No. 57: Analytical Method Validation and Transfer for Biotechnology Products.* Bethesda, Md.: PDA, 2012.

About the Author

Stephan O. Krause, PhD, is currently AstraZeneca's subject matter expert for analytical qualification, validation, and transfers and is the global specification committee secretary for all late-stage clinical and commercial biological products. He is a member of PDA's BioAB and will be teaching the new PDA Education course, "Analytical Method Qualification, Transfer, and Validation for Biosimilars," June 22, following the *2016 PDA Biosimilars Conference.* For more information, visit www.pda.org/2016BioCourses.

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BioAB Continues to Look Ahead

Another year is speeding past us and there is much activity at PDA. Strategic initiatives have been developed by the Board of Directors as part of the Strategic Plan that will drive the organization for the next five years. As I move from the position of Treasurer to Chair-Elect, I reflect on the strong position PDA has achieved in recent years, not just financially but also in accomplishing our mission of connecting People, Science and Regulation®. Through the strong leadership of the PDA staff, we continue to support the industry in many ways by providing training, technical guidance, and opportunities for networking in our industry. I can honestly say that I am very excited about where we are headed, building on our current achievements.

In 2016, we have already completed a successful Annual Meeting with well over 900 attendees. Attendees learned about innovative manufacturing technologies and concepts. From flexible facilities to continuous manufacturing, new technologies continue to arrive in our industry. Manufacturing science is definitely evolving at a very fast pace. To ensure the latest concepts and innovations in manufacturing science come to fruition for the biotech industry, the Biotechnology Advisory Board (BioAB) has taken on this topic as a strategic area along with its ATMP and biosimilars initiatives as outlined by **Melissa Seymour** in last month's "Voices of the Board."

In the area of cellular engineering, BioAB is looking to identify key areas where technical guidance is needed, and plans to leverage the upcoming ATMP meeting in Europe and previous ATMP conferences to delve further into this area. BioAB recognizes that these cellular therapies are innovative products with nontraditional development pathways. These are products that may at times be developed by hospitals and clinics, and as such, require technical information in the areas of GMPs and aseptic processing. These are core strengths of PDA that can benefit this sector of the biotechnology industry. For example, a technical report on autologous cell-based therapy control strategies is currently under development.

In the area of biosimilars, BioAB is exploring areas such as setting specifications, similarity to the reference product, validation and stability requirements. With two biosimilar products recently licensed in the United States and many already approved in Europe, PDA is poised to enter this arena to contribute to the technical and quality aspects of this topic.

In addition to these areas, BioAB is also addressing key scientific and technical areas such as the phenomenon known as "Low Endotoxin Recovery" (LER), viral contamination risk mitigation, mycoplasma filtration techniques, and reprocessing of biopharmaceuticals. As recent as the *2016 PDA Annual Meeting,* key industry experts met to benchmark and exchange experiences and data on LER to better understand the underlying mechanism and biological relevance of the phenomenon, and to discuss the potential cause-and-effect relationship of protein products.

BioAB is also in the process of reviewing older PDA technical reports with an eye toward identifying those that need updating to ensure the most relevant information is present in our technical teports.

Finally, BioAB is ready to assist in the PDA Manufacturing Science Program℠ to ensure that innovative technologies can be implemented in biopharmaceutical manufacturing. Stay tuned as this moves forward, and as always, if you are interested in volunteering for any of these topics, contact PDA's volunteer coordinator at volunteer@pda.org.

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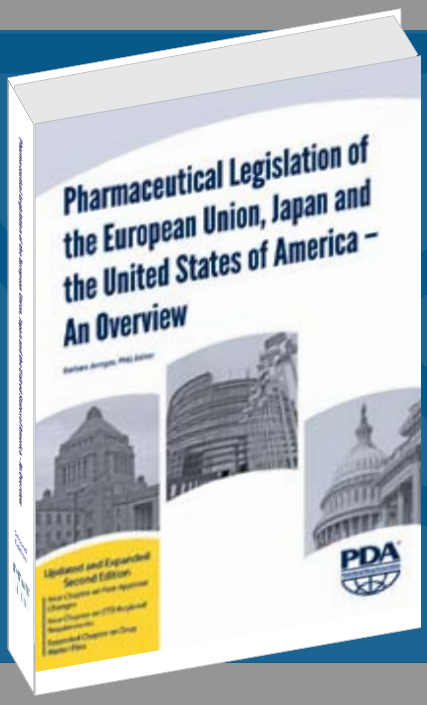

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editor's message

Manufacturing on the Move

This is the year of manufucturing at PDA, reflecting technological shifts taking place in the industry.

The Annual Meeting focused on several kinds of manufacturing innovations. In addition, PDA's Manufacturing Science Program[SM] held another meeting to advance its projects. PDA's Biotechnology Advisory Board (BioAB) has attuned its focus to innovations in manufacturing, including continuous manufacturing.

PDA's efforts reflect what is important to our members and the pharmaceutical industry at large. Continuous manufacturing, for instance, is starting to move from the "new technology" category to a bona fide technical trend. In April, the U.S. FDA announced that it had approved a manufacturer's change from a traditional batch production method to a continuous manufacturing system for the first time.

CDER's **Lawrence Yu** announced this decision on the *FDA Voice* blog. Noting that the transition from batch to continuous production is "not easy," Yu stated that the Agency "encourages others in the pharmaceutical industry to consider similar efforts." He cited the recently released draft guidance, *Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base,* as one tool that can help companies manage the regulatory aspects of such a change.

With Janssen Products' switch to continuous manufacturing for its HIV-1 drug and Vertex gaining an original drug approval for a cystic fibrosis drug using continuous manufacturing in 2015, it is only a matter of time before more companies make the switch.

PDA members will be right in the mix of all this activity, so keep an eye on the *PDA Letter*, the *PDA Journal of Pharmaceutical Science and Technology,* PDA's technical reports, conferences and courses to see what the Association is doing to help your company make the leap, whether it be from batch to continuous manufacturing, stainless to single-use systems, or innovations in aseptic filling or sterilization processes.

Maybe your company is interested in using Big Data to improve all your manufacturing processes, just as **Michele D'Alessandro's** team did to improve vaccine yields? This issue's cover story and three companion "On the Issue" videos can give you some insight on the value and challenges of using Big Data.

It is an exciting time to be in pharmaceutical manufacturing, and I look forward to hearing about all the great innovations rising to the surface from PDA's members!

PDA Letter

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

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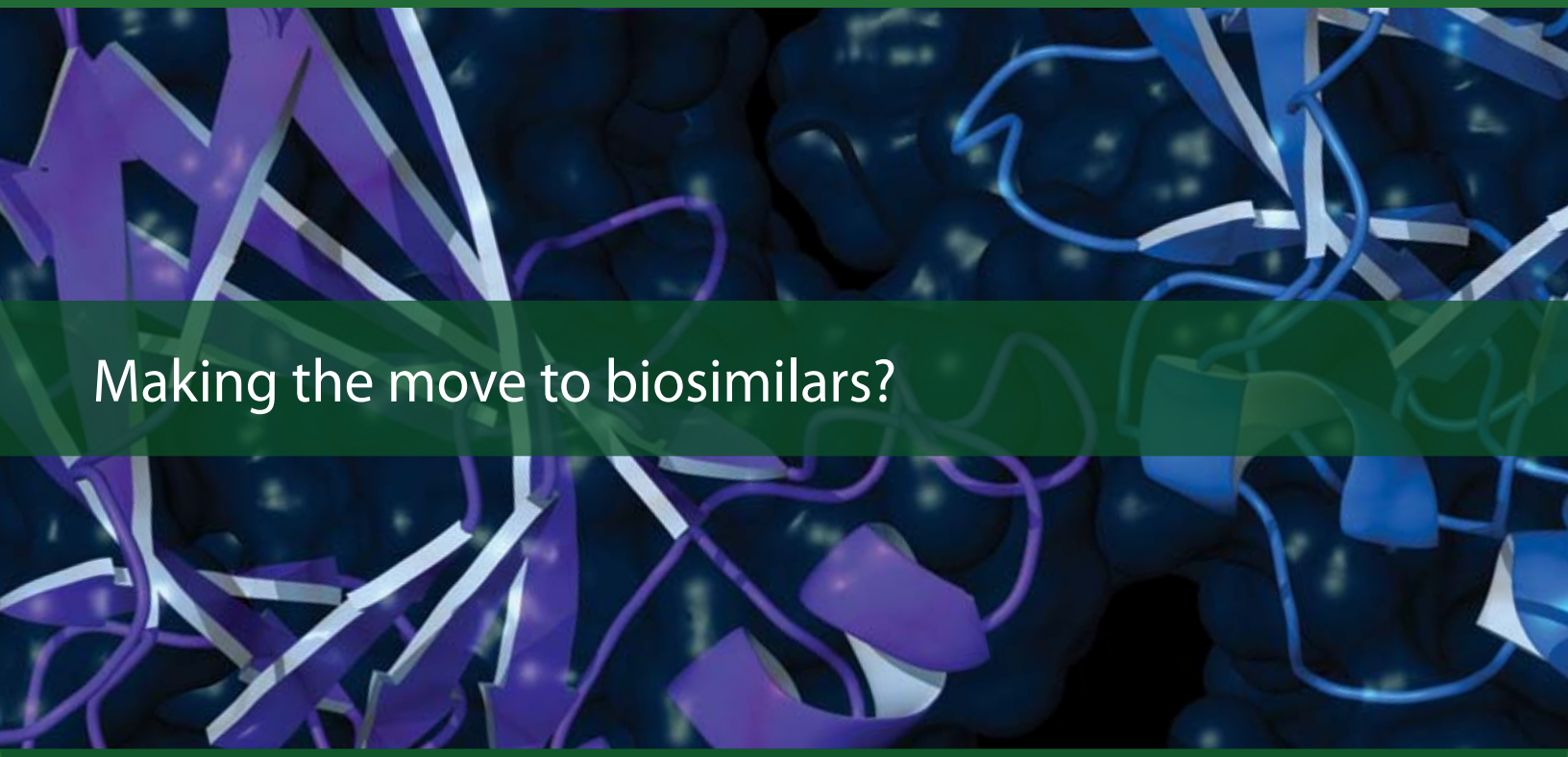

Making the move to biosimilars?

PDA is offering two new courses that will help you understand the challenges that must be considered before entering the field of biosimilar manufacturing.

The *Biosimilar CMC and Regulatory Challenges* course will help you gain insight into why biosimilars are not treated by the regulatory authorities as 'bio-generics' and understand the totality of what is required in bringing biosimilars into the marketplace.

Interested in learning how to generate suitable protocols and acceptance criteria and add to your regulatory submissions with ease? Then PDA's *Analytical Method Qualification, Transfer and Validation for Biosimilars* course is for you! This course will provide a practical and detailed overview on how to consistently perform risk-based analytical method qualification and validation for all method and product lifecycle steps. Instruction will build on ICH and local U.S. and EU guidance documents to provide more practical direction.

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The *2016 PDA/FDA Joint Regulatory Conference* agenda is filled with opportunities to expand your knowledge and network with colleagues. You can attend five plenary sessions, which include the ever-popular Compliance and Center updates; nine breakfast sessions; and 14 Interest Group sessions. Concurrent sessions will be offered in three concurrent tracks focusing on *Product Quality, Science & Innovation*, and *Lifecycle Management – Regulatory Challenges & Opportunities*.

To learn more and to register, visit pda.org/2016pdafda.

Immediately following the Conference, Sept. 14-15, the *2016 PDA Data Integrity Workshop* will be held. This Workshop will include a blend of presentations from regulatory and industry experts, case studies and round table discussions. Special focus on exploring the multiple facets of data integrity, such as quality culture, human behavior, training needs and technology requirements, will help attendees get a broad perspective on common factors, and cause and effect on data integrity issues.

To learn more and to register, visit pda.org/2016dataeast.

And, on September 15-16, PDA Education will host six courses to complement what you learned in the Conference and Workshop.

Course offerings include:

- *GMPs for Manufacturers of Sterile and/or Biotechnology Products* (September 15)
- *Establishing and Implementing an Effective GMP Auditing Program* (September 15)
- *Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations* (September 15-16)
- *Preparing for Regulatory Inspections for the FDA and EMA* (September 15-16)
- *Investigations – Best Practices* (September 15-16)
- *Managing the QC and R+D Laboratory in a GMP Compliant Manner* (September 16)

To learn more and to register, visit pda.org/2016PDACourses.

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Register before July 1 and save up to $600