People • Science • Regulation

PDA Letter

Volume LV • Issue 9 w.pda.org/pdaletter October 2019

Can We Reprogram the Human Computer?

CEO Jeff Galvin Believes We Can 26

2019 PDA Quality Week

Mastering Risk Management for Organizational Success

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HIGHLIGHTS OF THE WEEK

Tuesday, Dec. 10
Get the latest industry and regulatory perspectives on ICH Q9

Friday, Dec. 13
In this compliance update, regulatory experts will share their thoughts on the regulators' use of QRM

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- ***Building a Foundation and Culture for Quality Risk Management Integration Workshop*** **| December 11**
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- ***Optimizing Quality Risk Management Conference*** **| December 12-13**
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BUILDING A FOUNDATION AND CULTURE FOR QUALITY RISK MANAGEMENT INTEGRATION WORKSHOP: **DEC. 11**
OPTIMIZING QUALITY RISK MANAGEMENT CONFERENCE: **DEC. 12-13**
#PDAQualityWeek

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October 2019 PDA Letter

Can We Reprogram the Human Computer?

CEO Jeff Galvin Believes We Can

Rebecca Stauffer, PDA

What if developers of cell and gene therapies treated their products like software releases? What if the human body could be manipulated like a highly complex computer?

Jeff Galvin, CEO of American Gene Technologies, certainly has that mindset, frequently referring to cell and gene therapies as "reprogramming the human computer."

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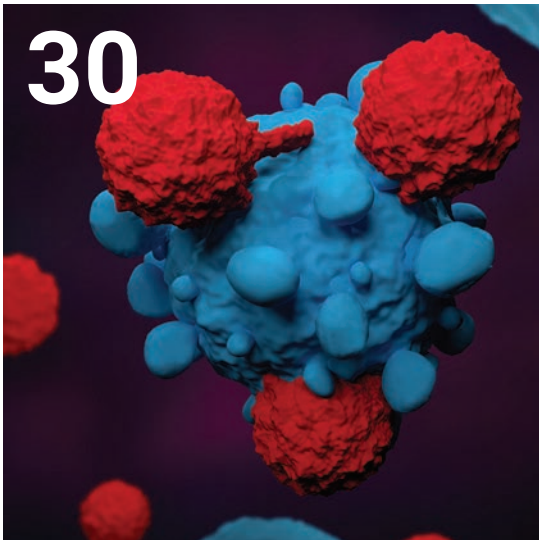
Kevin Allen Photography

Conference Puts Human Face on Cell and Gene Therapies

Rebecca Stauffer, PDA

Cell and gene therapies will unquestionably comprise a large part of biotech companies' portfolios in the upcoming decades. Unlike traditional large molecules, these products have different manufacturing and supply chain needs, requiring a fresh look at existing regulations. Yet these challenges will need to be addressed due to the promise of these products to cure a variety of diseases and disorders.



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InfoGraphic

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Process Approach Goes Global

Earlier this year, the European arm of PDA's Quality Systems Interest Group surveyed members of its process owner subgroup about how they have implemented the process approach at their companies.

PDA Letter

Volume LV • Issue 9 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.

Departments

Digital Exclusives

> **On the Issue** | A Particulate Matter Lifecycle Approach in Harmony with <1790>
Gateway Analytical's **Antonio Scatena** discusses USP <1790> at the *2019 PDA Visual Inspection Forum.*

> **On the Issue** | Here They Come: Pharma Students
Keck Graduate Institute Student **Lyanna Jauregui** discusses her poster at the *2019 PDA Annual Meeting* with the Southern California Chapter's **Jason Kerr.**

> Are Your RMM Organisms Reflective of Your Process?
Find out how you validate your rapid method.

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MARCH 30 – APRIL 1 | RALEIGH, NC
EXHIBITION: MARCH 31 – APRIL 1
WORKSHOP: APRIL 1-2
TRAINING COURSES: APRIL 3

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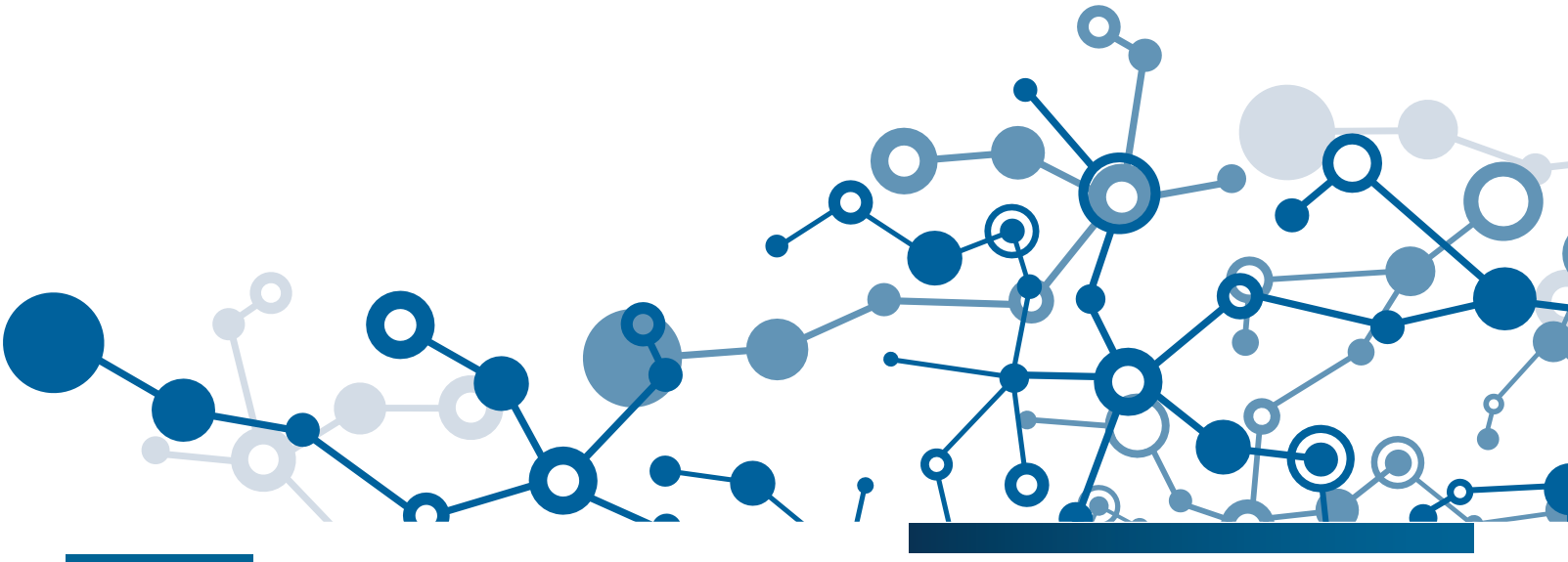
PLAN AHEAD FOR 2020

PDA 2020 Signature Conference Lineup Just Announced!

MARCH 30-APRIL 1	***2020 PDA Annual Meeting*** Registration now open!	Raleigh, NC
APRIL 21–22	***2020 PDA Visual Inspection Forum*** Registration now open!	Berlin, Germany
JUNE 9-10	***2020 PDA Europe Quality and Regulations Conference***	Dublin, Ireland
OCT. 5-6	***2020 PDA Universe of Pre-Filled Syringes and Injection Devices***	Las Vegas, NV
OCT. 19-21	***15th Annual PDA Global Conference on Pharmaceutical Microbiology***	Washington, DC



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Mark your calendars now for these important dates.

To get the latest updates on PDA's 2020 events, visit *pda.org/calendar*

Changes Coming to *PDA Letter*

Rebecca Stauffer @RebeccaStauPDA

Just as the cell and gene platform under development by **Jeff Galvin,** the subject of our cover story, represents revolutionary changes in the pharmaceutical industry, the *PDA Letter* continues to evolve as the publishing space grows ever more digitized.

With this in mind, I would like to announce some changes coming to the Letter. Not to worry, the *PDA Letter* will remain one of PDA's major member benefits with coverage of the latest scientific and regulatory developments in pharmaceutical manufacturing. Beginning next year, we will be reducing our print issues from ten issues a year to six. While print copy will be reduced there will be greater Web content each week.

Each print issue will contain articles that for the most part have already appeared online. Instead of one article a week posted to the website, there will be two to three articles (or videos) posted weekly.

I am very excited about these change and anticipate that there will be questions about this move. I can tell you that we will also be expanding our international content with articles targeting audiences in Europe and the Asia-Pacific region. We will produce PDFs collecting content for these regions. This content will be specific to the issues affecting those areas and may even feature articles in local languages.

We are expanding our content *not* diminishing it, so there will be more opportunities to be published in the Letter.

In addition, we are looking for volunteers to review *PDA Letter* article submissions and recommend topics for multimedia coverage as part of the *PDA Letter* Editorial Committee for the 2020–2021 term. If you are interested in either writing for the Letter or joining the PLEC (or both!), feel free to reach out to me. I am also looking for suggestions for other thought leaders like Jeff we could profile in future issues.

First PDA Standard Out for Public Comment

PDA proudly announces that its first draft standard, "BSR/PDA Standard 01-201x, Enhanced Purchasing Controls to Support the Bio-Pharmaceutical, Pharmaceutical, Medical Devices and Combination Products Industries," is available for public review and comment. The draft is open for review and commenting until Nov. 4, 2019. To receive your copy and to submit your comments, please make your request to standards@pda.org.

Martin VanTrieste, President and CEO, Civica, and PDA Past-Chair, and **Susan Schniepp,** industry consultant and former PDA Director, co-chair the committee behind this standard.

"Historically, in our industry the people who make the decisions on which suppliers to select in the negotiations of the contract are not in the quality unit or even manufacturing; they are in procurement or sourcing or a purchasing organization," Van Trieste said. "We feel it is important not only does everyone have to be involved in the quality of the product, that the people who actually make those decisions are held accountable and this new ANSI standard will help do that."

PDA is also advancing five other standards:

1. BSR PDA Standard 02-201x, Cryopreservation of Cells for Use in Cell Therapies and Regenerative Medicine Manufacturing

2. BSR PDA Standard 03-201x, Standard Practice for Quality Risk Management of Aseptic Processes

3. BSR PDA Standard 04-201x, Phage Retention Nomenclature Rating for Small and Large Virus Retentive Filters

4. BSR PDA Standard 05-201x, Consensus Method Rating for 0.1 Mycoplasma Reduction Filters

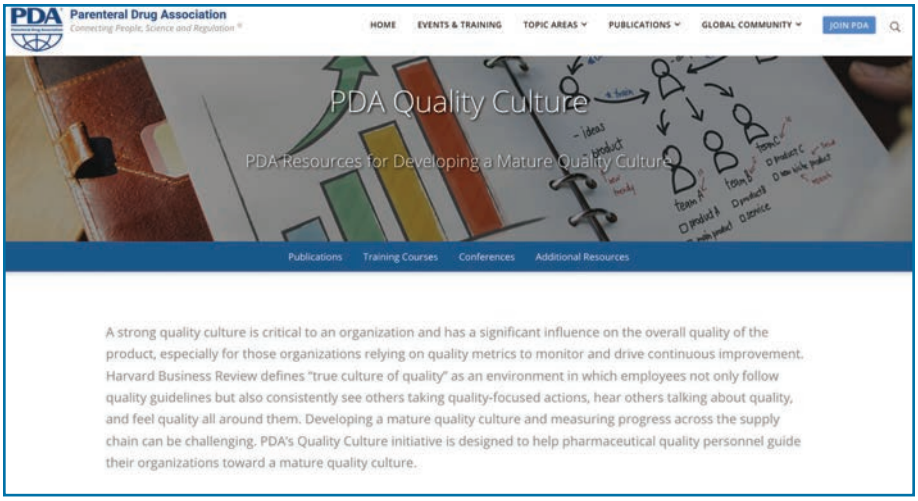
5. Quality Culture (pending ANSI approval)

More information about PDA's role in standards development can be found here: www.pda.org/scientific-and-regulatory-affairs/pda-ansi.

PDA Launches Quality Culture Website

As part of its quality culture initiative, PDA has just launched a new website featuring resources to help pharmaceutical quality personnel guide their organizations toward a mature quality culture. This website offers links to publications, training courses, conferences and additional resources on the topic.

The site can be accessed here: www.pda.org/scientific-and-regulatory-affairs/quality-culture.



PDA Volunteer Spotlight

Lisa Rutter

- **Director, Quality Head**
- ***Partner Therapeutics***
- Member Since | **2017**
- Current City | **Bothell, Washington**
- Originally From | **Janesville, Wisconsin**

When we are part of a great team, we know others have our backs

What led you to volunteer with PDA?
I wanted to establish a chapter in the Pacific Northwest. The California chapters have been so successful, creating many amazing opportunities for people on the West Coast.

At the same time, it was challenging for PDA members in the Pacific Northwest to attend meetings in California due to geographical constraints. I hope this new chapter creates the same environment that brings people, science and technology together. It has been a truly incredible experience to get our chapter kicked off through support from PDA and the other chapters. I am now the President of the Pacific Northwest Chapter.

Of your PDA volunteer experiences, which have you enjoyed the most?
Since I am still pretty new at this, I would say establishing the chapter, and, in particular, meeting our colleagues from both the Southern California and West Coast Chapters at the *2019 PDA Annual Meeting*.

How has PDA contributed to your career?
PDA has supported my continued education by allowing me to network with industry experts in both the quality and regulatory space. Attending the *PDA/FDA Joint Regulatory Conference* is a highlight for me each year since I can hear from both regulators and industry leaders on the latest manufacturing, quality, supply and compliance issues.

What lessons has your work taught you?
My work life has taught me many lessons over the years. The most important has been how to create and build a strong team. When we are part of a great team, we know others have our backs and we feel supported and encouraged. We rise to face challenges together, exchange ideas, work through roadblocks, deliver on time, celebrate successes and learn from the failures along the way.

What was the last book you read?
I just read an amazing book, *On Fire: The 7 Choices to Ignite a Radically Inspired Life,* by **John O'Leary.** I would love to meet the author. His message is one of inspiration and that "gratitude unlocks the fullness of life."

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Student Learns Firsthand About Industry

David O'Loughlin, Maynooth University

Earlier this year, I was honored to be one of two students awarded a scholarship to attend the *4th PDA Europe Annual Meeting* in the beautiful city of Amsterdam. The theme of this year's conference was "Global Healthcare of the Present and the Future." Having just finished the third year of my degree program in pharmaceutical and biomedical chemistry at Maynooth University, I was keen to see how technology is advancing in an increasingly digital and paperless age.

On the first day, members of PDA's Ireland Chapter met me in the exhibition area and showed me around. This allowed me to visit some of the exhibition booths.

As far as the sessions, I particularly enjoyed **Derek Duncan's** talk, "Ensuring Container Closure Integrity of Gene Therapy Products Needing Deep Cold Storage." Duncan works for Lighthouse Instruments, a company that designs non-destructive analysis equipment for determining the gas composition of the headspace. Their instruments can determine if CO2 has leached into gene therapy vials during storage on dry ice. CO2 ingress shows that during storage the vial has been compromised, which could lead to contamination of the product. I found all of this very fascinating!

Any system which can reduce the footprint required to develop these vaccines is extremely valuable

The other highlight of the conference for me was **Jose Castillo's** talk, "Low-footprint, Intensified, Single Use Platform for the Production of Viral Vaccines." His team at Univercells developed NevoLine, a viral vaccine production technology that cuts the footprint of a facility from 5000–10,000 square meters to 1500 square meters and they estimate the cost per dose will fall from U.S. $1.2-1.5 to U.S. $0.3 million. In a world facing a shortage of vaccines with a supply gap of around 50 million doses per year, any system which can reduce the footprint required to develop these vaccines is extremely valuable.

Other sessions also highlighted specific new technologies, including one on the implementation of blockchain technology into the pharmaceutical industry.

In addition, it was fantastic to get exposure to regulation in the industry. As a student, I have learned about the importance of regulation but had no firsthand experience of it. So, I found the keynote speeches from the U.S. FDA, EMA, MHRA and WHO representatives especially interesting.

I would like to thank the PDA Ireland Chapter for this wonderful opportunity, and I hope to stay involved with them into the future.

Valerio di Giovanni was one of the many speakers at the *4th PDA Europe Annual Meeting*

PDA Who's Who

Jose Castillo, Cofounder and Chief Technology Officer, Univercells

Valerio di Giovanni, Head of International Development WCC Adv. Manufacture, Altan

Derek Duncan, Director, Europe Product Line Lighthouse Instruments

pda.org/2019RapidMicro

2019 PDA Rapid Microbiological Methods Workshop

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EXHIBITION: OCT. 23-24
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PDA Photostream www.flickr.com/parenteral-drug

Advanced Therapy Medicinal Products Conference
June 4–5 | Vilnius, Lithuania

Thomas R. Kreil, PhD, Takeda

(l-r) Johannes Blümel, Paul-Ehrlich-Institut; Marc Eloit, PathoQuest; Martin Wisher, Merck KGaA, BioReliance

Attendees were offered an opportunity to tour the old town of Vilnius following Day 1 of the conference

(l-r) Alistair Gibb, UK MHRA; Margarida Menezes-Ferreira, Infarmed; Isabelle Bekeredjian-Ding, Paul-Ehrlich-Institut

PDA Photostream www.flickr.com/parenteral-drug

PDA Visitors
Bethesda, Md.

Members of PQRI's board convened onsite at PDA HQ on Sept. 12.
(l-r) Diane Paskiet, West; John Punzi, PhD, PQRI; Steven Tyler, PQRI; Jillian Brady, PQRI; Tina Morris, PDA

PMF Task Force met for a face-to-face meeting Sept. 19 (l-r) Anthony Perry, SCHOTT; John Ayres, MD, Pharma Safety Solutions; Jahanvi (Janie) Miller, PDA; Xu Song, BMS; Ravi Patel, West; Carol Rea Flynn, Corning

Members of the task force behind standard ASN-0003 Quality Risk Management met Sept. 19

(l-r) Hal Baseman, ValSource; Aidan Harrington, PhD, DPS Group; Kristen Anderson, PhD, U.S. FDA; Noel Long; Ed Tidswell, PhD, Merck; Darla Erman, CSL Behring; Frederic Ayers, Eli Lilly; Raji Vathyam, American Regent; Ivy Louis, Vienni Training and Consulting; Kelly Waldron, PhD, Valsource; John Kutney, Novavax; Anne Renton, Eli Lilly; Josh Eaton, PDA; Christine Roberts, PDA

Publishing Intern Expands Horizons at PDA

Madeline Cusick, Georgetown University

Before I arrived at PDA for my first day as the 2019 summer intern in the Publishing department, I anticipated the bulk of my days would be spent assisting with copy editing articles for the *PDA Letter.* To a certain extent, my expectations were accurate. While working under **Rebecca Stauffer,** Managing Editor of the *PDA Letter,* I gained invaluable knowledge about editing through both one-on-one tutorials and opportunities to work independently. However, the skills I will take away from this summer include far more than just how to adhere to AP style, make a paragraph more coherent or catch serial commas.

Most of my responsibilities involved assisting with the preparation for the July/August issue of the Letter. Although this involved plenty of copy editing, I also gained a more holistic insight into the preparation of a magazine, from mapping out the layout (on an actual map that hangs in Rebecca's office), to collaborating with **Katja Yount,** the Letter's graphic designer, about artwork accompanying the stories and going through the various "proofs," or stages of editing, leading up to the final, ready-for-print edition. Living in a word where media is increasing consumed online, I also saw how stories are promoted through email newsletters, like the PDA *news uPDAte,* and, sometimes even posted to the website ahead of print.

In addition to working on one particular copy, and perhaps more importantly, I witnessed how PDA is working to ensure the Letter remains invaluable to its readers by making changes to its format that reflect the world's rapidly changing patterns of media consumption. I was lucky enough to attend meetings where discussions took place on how the number of annual print copies would be reduced from ten to six in 2020 while at the same time increasing the frequency and quantify of online content. Witnessing changes like these unfold taught me the importance of keeping the big picture in mind.

Some of my other assignments included researching upcoming articles or preparing for interviews. One of these tasks focused on another popular trend in media: podcasting. Initially, I researched a variety of recording tools and software. I also listened to a variety of popular podcasts to compare the difference styles and brainstorm what would be best for a PDA audience. Finally, I helped Rebecca with recording a sample podcast through the Anchor podcasting app.

Aside from working on the Letter, attending a training course broadened my perspective about the scope of PDA's work. I was lucky enough to sit in on "Fundamentals of Aseptic Processing" and learn from both lectures and tutorials, including gowning demonstrations. It was fascinating to discover the level of detail that goes into keeping manufacturing environments sterile, especially because I could compare these practices to my work in EMS. When I am not at work or school, I spend my free time volunteering as an EMT, which required going through a HazMat operations course. During these classes, I learned how to suit up to protect myself from contamination, so I confess that I went into "Fundamentals" thinking I knew what to expect. Instead, I discovered the vast difference and heightened complexity between protecting an individual from contamination and keeping every aspect of an environment free from contamination.

For all the things that I learned, I also feel fortunate that I was offered the opportunity to make some contributions to the *PDA Letter.* For instance, I received a byline for an article and helped draft a few other short pieces. In addition, I assisted with writing a few press releases. Completing tasks like these helped raise my confidence in my writing skills.

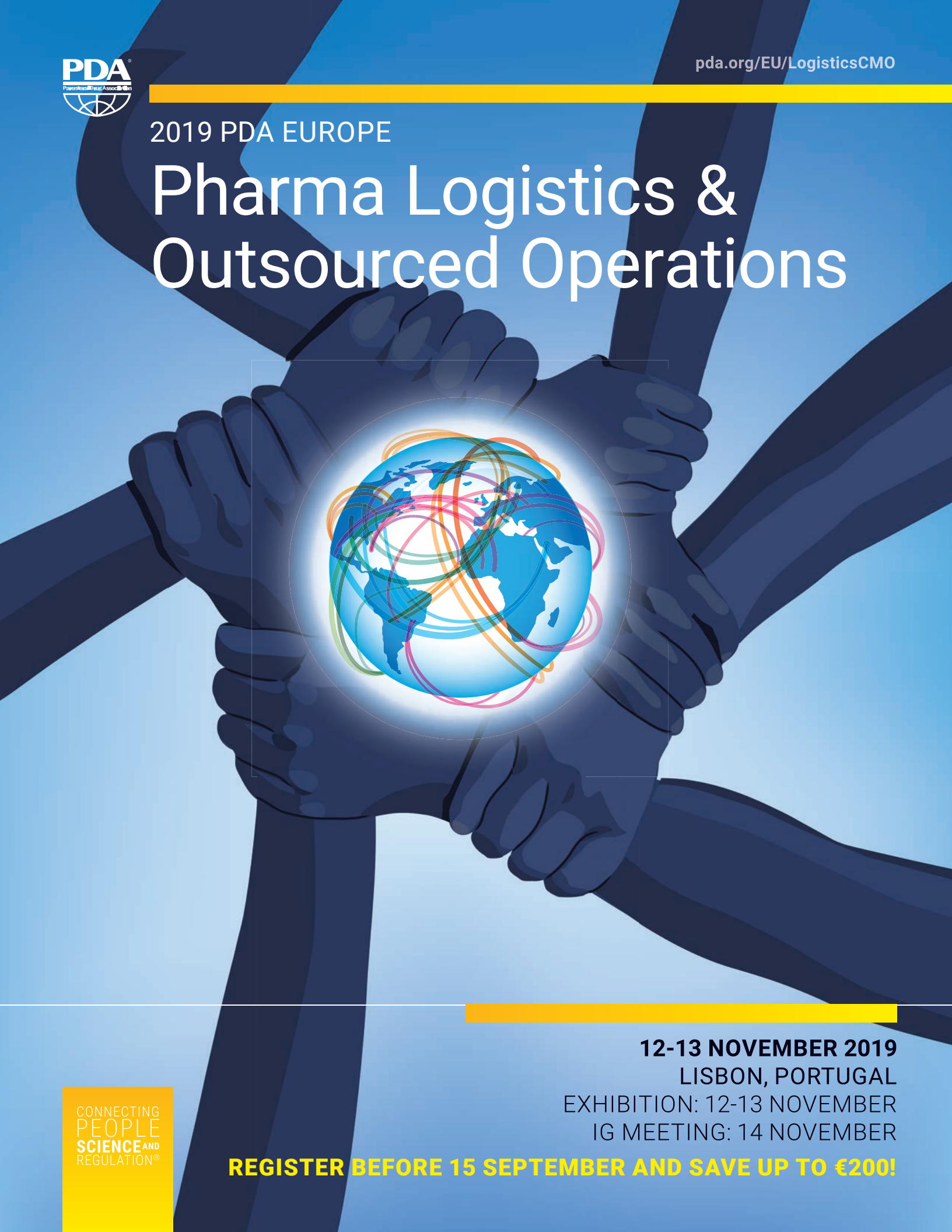
As I head back to school this fall, I'm excited to return to the classroom armed with the lessons I have gathered from my summer at PDA.

I also feel fortunate that I was offered the opportunity to make some contributions to the PDA Letter

pda.org/EU/LogisticsCMO

2019 PDA EUROPE

Pharma Logistics & Outsourced Operations



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LISBON, PORTUGAL
EXHIBITION: 12-13 NOVEMBER
IG MEETING: 14 NOVEMBER

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Interest Group *Corner*

Adventitious Virus Detection Tech IG Activities Prove Infectious at 2019 PDA Virus Safety Forum

The co-chairs of the Adventitious Virus Detection Technologies Interest Group provided an update on the group's activities during the interest group session at the *2019 PDA Virus Safety Forum,* May 8, in Long Beach, Calif.

Currently, the interest group is divided into three subgroups, each focused on one of the following deliverables: experimental protocols, a reference database and pipeline analysis and follow-up strategies.

The subgroup focused on experimental protocols is working on sample preparation related to viral detection using next generation sequencing, this includes identifying standards and reference materials that can be used for spiking studies to evaluate the performance of next generation sequencing. At this time, the subgroup is discussing a new spiking study to explore transcriptomics to evaluate detection of infected cells among a background of uninfected cells.

The second subgroup is tasked with identifying gaps in the new Reference Virus Database, a database developed within CBER at the U.S. FDA. This subgroup is developing criteria for a well-characterized database to support next generation sequencing analysis, identifying additional databases and working with the third subgroup on annotation.

The third subgroup is evaluating the characteristics of a good bioinformatics pipeline and designing best practices for follow-up investigations of next generation sequencing signals. In addition to working with the second subgroup on annotation, this subgroup is establishing ranges of bioinformatics criteria and thresholds for a positive hit, identifying the sources of background signals and how to control for them, developing controls for an assay that might facilitate follow-up investigations and assessing the effectiveness of laboratory follow-up procedures on representative contaminant.

The mission of the Adventitious Virus Detection Technologies Interest Group is to "advance next generation tools for viral risk evaluation by providing an informal, scientific forum for discussions and scientific collaborations." The group's current focus is next generation sequencing. For more information and to join, visit community.pda.org/#/group-overview?communityID=3982.

Journal *Top 10*

Particulate Matter Papers in Top 5 of Most-Read PDA Journal Articles

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

1. **PDA Paper**
   "Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products"
2. **Research**
   "Quality Risk Management Competency Model—Case for the Need for QRM Competencies"
3. **PDA Paper**
   "Achieving 'Zero' Defects for Visible Particles in Injectables"
4. **Review**
   "Particulate Matter in Injectable Drug Products"
5. **Research**
   "Measurement of Equilibration Time of Dry Goods Loads in Autoclaves"
6. **Research**
   "A Mechanistic Understanding of Polysorbate 80 Oxidation in Histidine and Citrate Buffer Systems—Part 2"
7. **Technology/Application**
   "Provable Data Integrity in the Pharmaceutical Industry Based on Version Control Systems and the Blockchain"
8. **Technology/Application**
   "Comparative Leachable Study of Glass Vials to Demonstrate the Impact of Low Fill Volume"
9. **Technology/Application**
   "Enabling Robust and Rapid Raw Material Identification and Release by Handheld Raman Spectroscopy"
10. **Conference Proceeding**
    "PDA Biosimilars Workshop Report (September 27—28, 2018) — Getting It Right the First Time for Biosimilar Marketing Applications"

Avoid Unmixed Process Solutions

Design and Execution of Solution Mixing Studies for Biopharmaceutical Production

Dosung Kim, Jeonghun Kim, Kwangjun Yoon, Denis Rigolet and Anthony R. Newcombe, Polus, Inc.

When it comes to mixing studies, what is an effective strategy and what factors should be analyzed?

Efficient mixing of processing solutions is critical to ensure process consistency and comparability. Although biopharmaceutical processes may use a large number of process solutions and vessel configurations ***(1–3),*** mixing validation is typically not undertaken at production scale for every solution. Instead, a risk assessment may be completed to identify the risks or impacts associated with the factors needed to dissolve chemicals used for solution preparation ***(4).*** The results of this assessment are then used to identify which representative buffer solutions require validated mixing studies. This process offers a high degree of confidence that all solutions used will be homogenous and appropriately mixed.

This process offers a high degree of confidence that all solutions used will be homogenous

Factors evaluated as part of the risk assessment may include, but are not limited to, solute type, solubility within the solvent, final solute concentration, agitator speed, vessel size, temperature and mixing time.

Reagent properties (such as viscosity, density and potential to foam) may also need to be considered, although as buffers used for biopharmaceutical production are gen-

erally dilute aqueous solutions, no significant issues are typically encountered and such factors are often discounted if supporting data is available **(Table 1).** One exception may be formulation buffers, as some excipients, such as polysorbate may result in some potential solution foaming. This impact, however, can be minimized by preparing a concentrated stock solution and adding the required supplementary liquid to the formulation tank.

Where possible, the temperature used for mixing validation is typically at the low end of the controlled temperature range of the media/buffer preparation environment used for solution preparation. This represents worst-case conditions, provided that dissolution of the solids in question is slower at reduced temperatures. With this strategy, the risk of minor temperature fluctuation on solution mixing during routine operations is mitigated and temperature variation is often discounted as a potential risk factor.

The agitation rate used for mixing validation is often determined prior to beginning the studies. An appropriate mixing speed and range (± 10%) is often identified during commissioning and qualification of the mixing vessels and this data may be used to define the range to be evaluated. A fixed agitation set point and the acceptable tolerance is usually tested with one mixing study at the set point, one and the higher speed (+10%) and one at the lower mixing speed (-10%).

The appropriate range of the mixing speed should be considered as part of validation studies, particularly when solutions may demonstrate excess foaming or when aeration could affect the stability or properties of the solution components. At least three significant factors are typically associated with the solids used for preparation of buffers and solutions for biopharmaceutical production—solubility, concentration and the fill volume of the vessel used for solution preparation **(Table 1).**

The vessel size, dimensions and solution fill volume may have an impact on the mixing of process solutions and the fill volume to be used for routine solution preparation should be used for mix-

The agitation rate used for mixing validation is often determined prior to beginning the studies

Table 1 Risk Assessment Factors Typically Evaluated for Solution Mixing Studies

Impact Factor	Comments
Solubility	The property of a solid (or liquid) to dissolve, usually in an aqueous solution. The solubility of a substance depends on the physical and chemical properties of the solute as well as the temperature and the pH of the solution. Solubility data for each is usually obtained from relevant literature, such as the Merck Index ***(5)*** or United States Pharmacopeia ***(6).***
Concentration	The final concentration of a solution constituent will impact the duration of the mixing time required. Longer times will be required if the solutions are close to saturation. The maximum concentrations of each buffer constituent are typically assessed as part of the risk assessment.
Fill volume	Risk-based on nominal fill volume (%) in the solution preparation vessels. As the reagent quantities will be proportional to the volume prepared, the worst case will depend on the potential to cause foaming and vortex formation as this may impact the stability or properties of the solution components. Minimum volumes are defined that fully immerse vessel agitators.
Viscosity	This may impact the dissolution time for liquid solutes in finalized solutions. As most buffer solutions are relatively dilute, viscosity is generally not considered a critical factor.
Density	Buffer solutions typically have densities close to 1g/cm^3, therefore, density is not generally considered a critical factor.
Foaming	Most buffer solutions do not generate foaming, although this factor may need to be considered for media preparation.
Vessel geometry	Vessel geometry will impact solution mixing. Diameter to height ratios are evaluated, differences in impeller size and geometries are considered usually negligible. A simple risk assessment should be performed, however, to confirm the negligible impact of the geometry. The use of different mixing vessels usually presents little or no risk with respect to solution mixing.
Agitation rate	Agitation rate will impact buffer mixing. Typically, a fixed agitation speed is defined (with a minor variation in speed evaluated ie +/- 10%). The mixing speed is generally not considered a critical factor.
Temperature	Solutions are generally prepared within GMP facilities at ambient temperature. Ideally, mixing studies should be undertaken at the lower end of the ambient temperature range, but this is often not technically feasible. The temperature of the water used for solution preparation is more likely a factor.

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ing validation. Smaller volumes may be considered more of a risk due to a higher concentration of potential leachables ***(5)*** during storage if the solutions are subsequently transferred into disposable bioprocess bags. The risk of differences in the vessel geometry used for solution preparation are often not significantly different as vessels typically have a similar height to diameter ratio. Additional risk assessments, however, may be required to evaluate the impact of vessel size on solution mixing.

Once the highest risk buffer solutions have been determined, at least one technical study is usually undertaken within the production scale vessels for each worst-case solution identified. The purpose of the technical studies is to determine the mixing times that will be subsequently validated for routine manufacturing. To evaluate mixing, samples are taken and analyzed (pH, conductivity, osmolality) at routine intervals (for example five minutes) or, preferably, evaluated using real-time monitoring ***(2);*** measurements used to confirm solution homogeneity should be included as part of the mixing study. The mixing time to be validated is often determined when a minimum of three consecutive time points all meet the required specifications.

Keep in mind that pH alone is not evaluated for the mixing study. In fact, the pH may meet the desired range when the solution is formulated only after a small number of solids have dissolved. It is also important to define a minimum time for charging of the solids into the vessel as this additional time contributes to the solution mixing and may underestimate the mixing time required. Also, the procedure for incorporating each solute should be established. A visual inspection of the mixing vessel during mixing through viewing ports is also recommended. This ensures no visible solids are present at the end of the mixing time. If a sample port is used, additional samples may also be taken and analyzed when mixing has stopped. The solution vessel is then emptied to provide further assurance that the solution is homogenous throughout the vessel.

Following the outcome of the mixing study, the mixing of individual solutions is validated using a minimum of three consecutive mixing studies at full scale. This process can help ensure consistency and comparability of the mixing process.

The appropriate range of the mixing speed should be considered as part of validation studies

Keep in mind that pH alone is not evaluated for the mixing study

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2019 PDA Upcoming Events

OCTOBER

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

23-24 2019 PDA Rapid Microbiological Methods Workshop
Rockville, MD | *pda.org/2019rapidmicro*

25 PDA Global Conference on Pharmaceutical Microbiology Training Course Series
Rockville, MD | *pda.org/2019MicroTCS*

- **25** Exclusion of Objectionable Microorganisms from Pharmaceutical and OTC Drug Products
- **25** Establishment of a Risk-Based Environmental Monitoring Program
- **25** Contamination Control, Clean Room Design, and Environmental Monitoring for Controlled Environments – Option 2
- **25** Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Validation, and Ongoing Control
- **25** Application of Quality by Design and ICH Q9 Rules to Aseptic Processes and their Impact to Sterility Assurance
- **25** Developing a Microbial Monitoring Plan and Leveraging New Technologies for Effective Sterility Assurance in Aseptic Processes
- **25** The Microbiology of Water in a GMP Environment
- **25** Identification of Fungi for Quality Control

22-23 The Universe of Pre-Filled Syringes and Injection Devices
Gothenburg, Sweden | *pda.org/EU/UPS2019*

- **21** Impact of Pre-Filled Syringe Components on Biopharmaceuticals Workshop
- **21** Innovating the Journey from Manufacturing to the Patient Workshop
- **21** Innovative Drug Delivery Systems/Combination Products Workshop
- **24-25** All about Pre-Filled Syringe Systems – From Initial Development to Final Fill Finish
- **24-25** Extractables and Leachables – Fall Edition
- **24-25** Container Closure Integrity Testing – Fall Edition
- **24-25** Measuring Quality Culture Maturity? Learn How!
- **24-25** Test Methods for Pre-Filled Syringe Systems – Fall Edition

28-29 Cleaning Training Course Series – Option 1
Bethesda, MD | *pda.org/2019CleaningTCS1*

- **28** Addresssing Biofilm and Other Non-Routine Microbial Events
- **29** Shutdown Recovery and Disinfectant Effectiveness Studies for Controlled Environments

28-30 Airflow Visualization Techniques and Practices ■
Bethesda, MD | *pda.org/2019airflow*

29-30 PDA Pharmaceutical Product Quality Testing Conference
Tokyo, Japan | *pda.org/2019japan*

- **10/31-11/1** Extractables and Leachables for Parenteral Applications – Japan
- **10/31-11/1** An Introduction to Visual Inspection – Japan

29-30 Characteristics of Pharmaceutical Elastomers and Aluminum Seals in Parenteral Packaging Systems
Middletown, DE | *pda.org/ParenteralPackagingTC*

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

NOVEMBER

6-8 Train the Trainer Training Course Series
Bethesda, MD | *pda.org/2019TrainerTCS*
- 6 Designing/Presenting GXP Training Programs to Meet FDA Requirements
- 7-8 Learning, Knowledge Management, and Impact: Moving from Theory to Practice

7-8 Isolator Technology – Option 2
Bethesda, MD | *pda.org/2019IsolatorTech2*

11-15 Quality Risk Management Certificate Program – Option 2
Bethesda, MD | *pda.org/2019QRM2*
- 11 Foundations of Quality Risk Management
- 12-13 Quality Risk Management: Risk Control and Risk-Based Decision-Making
- 12-14 Practical Application of Quality Risk Assessment Tools
- 15 Quality Risk Management for the Design, Qualification, and Operation of Manufacturing Systems

12-13 2019 PDA Drug Delivery of Injectables Conference
Taipei City, Taiwan | *pda.org/2019taiwan*
- 14-15 Drug Delivery Device and Combination Product Risk Management and Safety Assurance Cases
- 14-15 Extractables and Leachables for Parenteral Applications
- 14-15 Fundamentals of an Environmental Monitoring Program

12-13 Pharma Logistics and Outsourced Operations
Lisbon, Portugal | *pda.org/EU/LogisticsCMO*
- 14 Supply Chain Management Interest Group Meeting

12-14 TR No. 62: Recommended Practices for Manual Aseptic Processes Training Course
Bethesda, MD | *pda.org/2019TR62training*

18-22 Cleaning Training Course Series – Option 2
Bethesda, MD | *pda.org/2019CleaningTCS*
- 18-19 Fundamentals of Cleaning and Disinfectant Programs for Aseptic Manufacturing Facilities
- 20-22 Validation of Biotechnology-Related Cleaning Processes

20-21 Strategies for Formulations Development – How to Get the Right Data in the Right Amount at the Right Time
Bethesda, MD | *pda.org/2019Strategies*

26-27 Single-Use-Systems: A New Age of Drug Making
Göttingen, Germany | *pda.org/EU/TC-SUS19*

NOVEMBER SPOTLIGHT ON:

2019 PDA QUALITY WEEK
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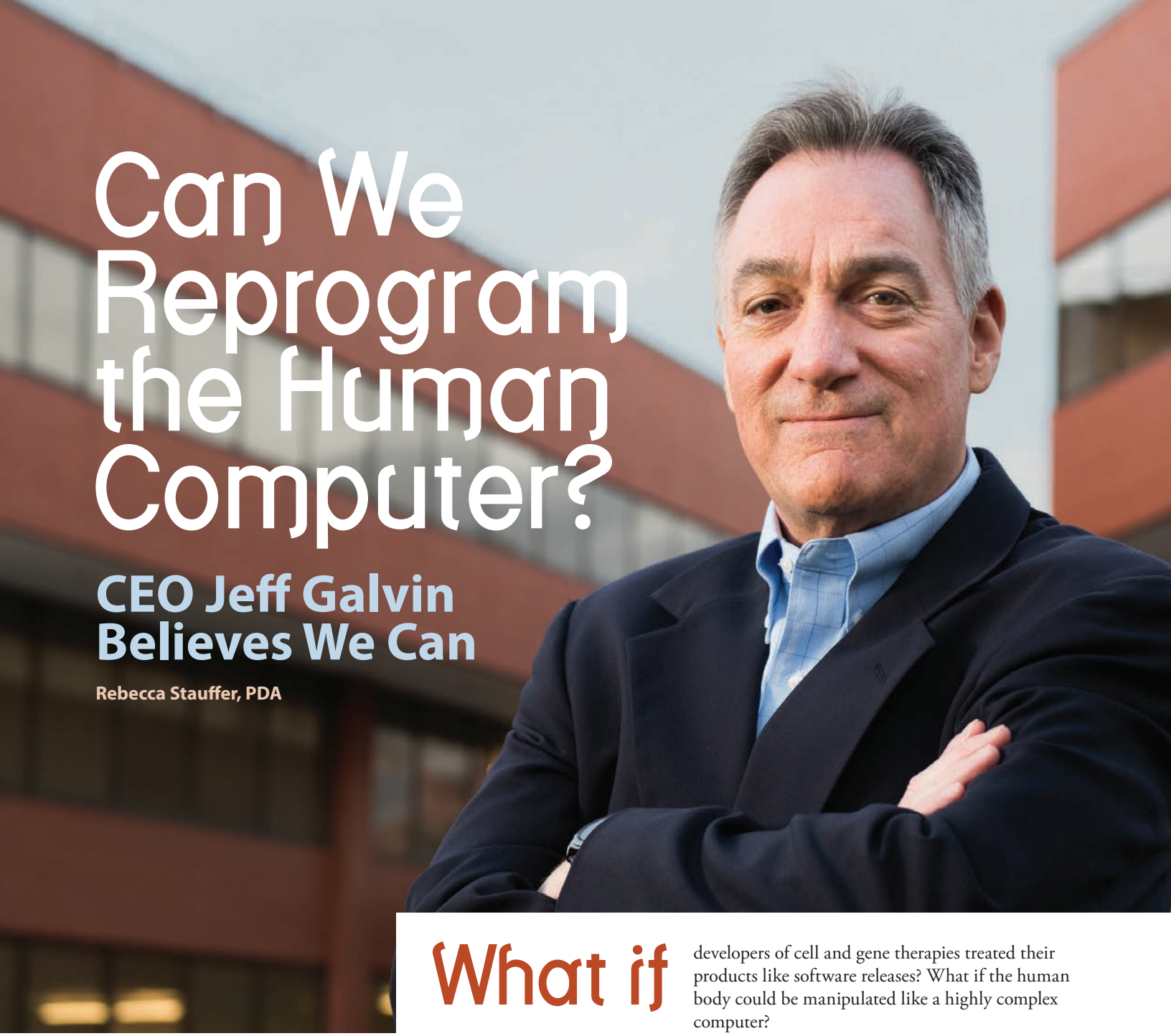
- 9-10 2019 PDA Risk Management in the Regulatory Landscape Conference
- 11 2019 PDA Building a Foundation and Culture for Quality Risk Management Integration Workshop
- 12-13 2019 PDA Optimizing Quality Risk Management Conference

■ This course is taught in PDA's U.S. Manufacturing Training Facility.



Can We Reprogram the Human Computer?

CEO Jeff Galvin Believes We Can

Rebecca Stauffer, PDA

What if developers of cell and gene therapies treated their products like software releases? What if the human body could be manipulated like a highly complex computer?

Jeff Galvin, CEO of American Gene Technologies, certainly has that mindset, frequently referring to cell and gene therapies as "reprogramming the human computer."

"I think this is a software industry, it is the software of DNA," he explains. "It has a lot of parallels to digital computers and software. I think digital has come to drug development, and analog days are going to end."

Galvin speaks from experience. He spent much of his career in Silicon Valley, including a five-year stint at Apple, where he remembers seeing **Steve Jobs** in his early days walking between office buildings in sandals and ripped jeans. Following his work at Apple, he spent many years working for startups in the Valley, ultimately, retiring at the age of 41. But after four years, he says "I needed more stimulation for my brain."

He started receiving a multitude of business proposals, but none piqued his intellectual curiosity.

Enter **Dr. Roscoe Brady.**

> **These are the PC days of gene and cell therapy. The future is the iPhone where curing a disease is like creating an app**

At the time, Dr. Brady, already a renowned researcher known for his pioneering work on manufacturing and delivering to patients the enzymes behind some genetic disorders, was researching the use of viral vectors to modify genetic structures in cells to potentially cure Gaucher disease and other rare, metabolic disorders as part of the National Institutes of Health (NIH). Galvin was intrigued by the technology and could see its promise. Dr. Brady had cutting-edge lentiviral vector research and discovery, and Brady eloquently articulated the way modified viruses could be used to modify DNA in cells, and how that technology could be brought to the clinic.

Galvin was excited about viral vectors and "smitten" with Brady. He then learned that Dr. Brady's lab was being shut down and felt the need to act, telling Dr. Brady that he thought NIH "may be shelving one of the most important things" he had ever seen. Galvin saw the potential for this treatment to address a multitude of diseases.

"We may finally be able to send radiation and chemotherapy the way of bloodletting and leeches, because there has got to be a better way than beaming cancer-causing radiation through your body to cure cancer."

Article at a Glance

- American Gene Technologies' CEO draws on Silicon Valley background as head of small biotech startup
- Company's platform uses viral vector technology
- Platform could be licensed to pharma companies

Although Galvin did not possess a traditional biotech background, he convinced Dr. Brady and the other researchers that his Silicon Valley background would be an asset, offering a new way of looking at gene therapies. He compares the human body to a computer, and Dr. Brady's platform to software.

"Well, it has a layer just like software. You have the transport layer, which is the viral vectors. [which are like] diskettes, tape or punch cards. They are the way you communicate with the human cell. But without something on them, they are nothing. On the next layer up are tools and components that can be efficiently combined in a myriad of different ways to cure a cornucopia of diseases. Then, after that, you build applications on top."

DNA Valley

Like his former boss at Apple, Galvin sounds prophetic in describing where he believes this technology is heading: "These are the PC days of gene and cell therapy. The future is a platform, like an iPhone, where curing a disease is like creating an app." And like Apple, he sees American Gene Technologies as one of many companies in Maryland's "Biotech Corridor" as the foundations to a future "DNA Valley."

Galvin founded American Gene Technologies in 2008. The company's mission is to "get the power of gene and cell therapy to maximum patient populations as quickly as possible because these are potentially life-saving technologies that could end a huge amount of human suffering."

This singular focus to offer gene and cell therapies "to the most people as quickly as possible is our mission. That brings the whole thing full circle."

He chose to locate the company in Rockville, Md., due to its proximity to the National Institutes of Health and other government research centers. This meant moving East from his Silicon Valley roots. Galvin notes many parallels between the early days of Silicon Valley and Maryland's Biotech Corridor.

"There are a lot of good things about the Maryland environment that make it the epicenter of gene and cell therapy," Galvin says. "This is where all the technology originated. The Human Genome Project was a quarter of a mile from here."

He sees the future of biotech becoming oriented to this region of the country, predicting that the corridor between Baltimore and Washington, D.C. will become known as "DNA Valley."

Hacking HIV to Heal Patients

The company's viral vector platform contains thousands of banked lentiviral vectors with a myriad of characteristics. These vectors can replace missing or damaged genes, prevent genes that cause disease and even kill cells. Additionally, American Gene's portfolio includes ImmunoTox™, a viral vector platform that reprograms tumor cells to stimulate gamma delta T-cells. These T-cells then kill the tumor cells and circulate through the bloodstream to kill secondary tumors.

He is particularly excited about the company's experimental therapy for HIV.

"For HIV, we are using a 'cell therapy' to improve the immune system to naturally suppress and eliminate HIV in the patient's body. First, we need a viral vector, and that is true about all gene therapies, you need some vector production, viral particle production, and then, in the case of a cell therapy, we need to figure out how you are going to consistently manufacture the cell product. One part of the cell product manufacturing process is infecting it with a viral vector in order to make the DNA modifications to improve the cells and make them ready

to go back into the body. The improvement we make in HIV is to 'harden' the HIV-specific T-cells so that they can't be infected by HIV virions they find in the bloodstream. That way, they can kill the virions instead of becoming infected.

"What we do with HIV is quite simple from 50,000 feet. You have HIV T-cells in your body and yet they cannot protect you from HIV. With a little teeny bit of improvement, they can. That is our product," Galvin explains.

"We know what the improvement is. We made a cell therapy, a protocol, that allows us to implement that whole thing in a very efficient manner and we can turn out something that can cure an HIV patient, for a cost figure where it is way cheaper to cure them than it is to treat them for the rest of their lives."

While on first glance, viral vectors may seem like CRISPR, he is emphatic that the two are quite different, using the term "add-gene" to describe viral vector therapy while CRISPR is a gene editing technology.

"The lentiviruses we use to modify cells are capable of integrating a new genetic construct into your existing genome. They do not chop anything out and replace it, they just add something," Galvin says. "It [viral vectors] has been around for over 30 years. It is very reliable...choose the right tools for the solution and you will have an efficient and reliable solution for a patient. That is the future of medicine."

The company expects to submit the IND for this HIV therapy soon and begin recruiting patients for clinical trials before the end of the year. It was in the midst of all this preparation that Galvin met with *PDA Letter* staff in a conference room at the company's headquarters on a relatively cool August afternoon. There is no production going on at the headquarters, as AGT uses two contract manufacturing organizations (CMOs), one in New Jersey for the cell process, and one only a few miles away in Gaithersburg, Md. that produces the lentiviral vector. At this time, the company plans to use a different CMO for each drug they produce.

> **"In fact, he even sees his drug products being delivered over the Internet"**

In another parallel to the IT world, Galvin sees his company as following more of a licensing model—he even goes so far as to refer to his researchers as "developers. Companies could in essence, "license" his viral vector platform to produce their own products, much like software companies did in the 1990s.

"I picture somebody else doing the Phase III and the commercialization," he says. Further, "everybody has their role in the future of medicine."

And when it comes to scale-up "we have to have a plan for that, but we do not have to implement it."

Real-Time Updates to Drug Products

As Galvin looks ahead, he sees his portfolio of products as a game changer. In fact, he envisions hospitals around the world purchasing a $200,000 piece of equipment that can be used to produce the HIV treatments onsite.

"It [the equipment] does not require a cleanroom to operate," he says. "They have to maintain this GMP equipment, but everything is reusable and disposable on this thing."

He compares this model to a software company working with vendors to support hardware such as server farms and ethernet boxes.

"You need to decide what is your core competency, and how you can maximize that," Galvin reasons.

"We are going to have to deal with this distributed network at some point, and it will evolve. It will not happen overnight, but I think initially there will be one manufacturer, and it may even be us that makes the lentiviral vector," he says. "It will not matter if you are in Africa getting treated or whether you are in the United States getting treated, you will be taking the same lentiviral vector. But with the cell manufacturing, it may make sense to move that in the near-term closer to the patient."

In fact, he even sees his drug products being delivered over the Internet. How? In the future, the equipment used to produce the product will receive automatic updates, much like a Tesla or even a smartphone.

"If there is a manufacturer in India, and we update our drug to version 2.1, why should they not have the latest and greatest?" he asks. "We can push the new design, which is really just a sequence, to every manufacturer in the world. They will download it over the internet. And guess what? It will turn out that the new protocol in these automated machines that are treating [patients], give you 10% more HIV-specific CDC positive T-cells that are immune to HIV than they used to with the old viral vector."

He points to Tesla, as an example. "The car is less and less hardware, and more and more software."

"Apple-Level" Excitement

Not only is the industry side changing but Galvin forecasts changes in the U.S. FDA regulatory approach as well. His company primarily works through CBER and has found that Center to be open to innovative approaches while taking risks into account. He expects CBER and other FDA centers to move to a simulation approach where a proposed human gene therapy will be simulated in a computer, giving regulators an opportunity to look for potential areas of concern.

Continued at bottom of page 42

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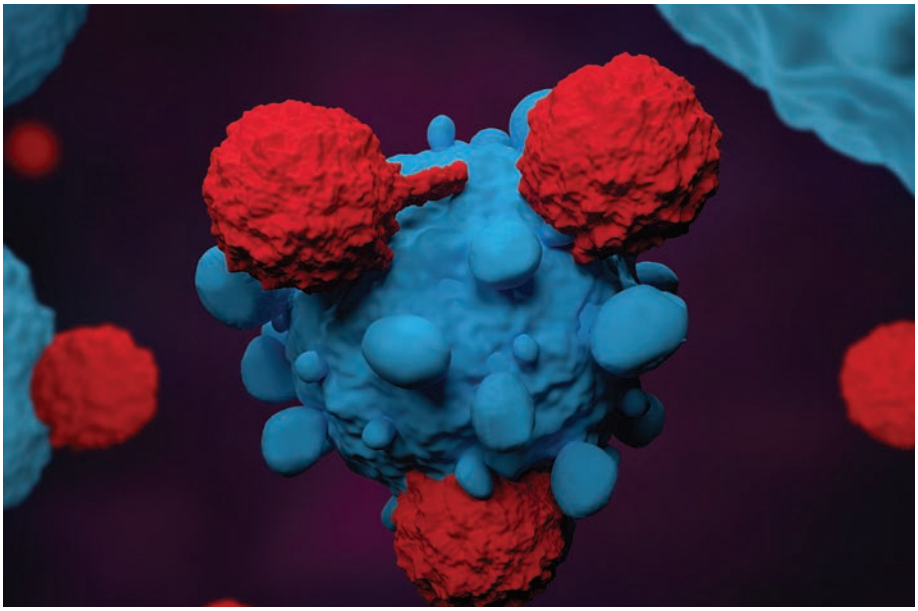
Conference Puts Human Face on Cell and Gene Therapies

Rebecca Stauffer, PDA



Cell and gene therapies will unquestionably comprise a large part of biotech companies' portfolios in the coming decades. Unlike traditional large molecules, these products have different manufacturing and supply chain needs, requiring a fresh look at existing regulations. Yet these challenges will need to be addressed due to the promise of these products to cure a variety of diseases and disorders.

The opening talk of the *2019 PDA Cell and Gene Therapy Conference* in Long Beach, Calif. on May 6 illustrated this last point in particular. **Tom G. Whitehead,** cofounder of the Emily Whitehead Foundation, put a human face to the often academic and technical discussion around commercialization of cell and gene therapies. At the age of five, his daughter, **Emily Whitehead,** was diagnosed with acute lymphoblastic leukemia (ALL). While most cases have an 85 to 90% cure rate, her case was more aggressive than usual, and she relapsed several times to the point her medical team recommended hospice care.

Her parents instead enrolled her in a Phase I clinical trial where her T-cells were reprogrammed to attack the cancer cells and then infused back into her bloodstream. Despite some initial setbacks, the therapy worked. Today, Emily remains in remission seven years later. She is recognized globally as the first pediatric patient cured via a T-cell therapy.

There was not a dry eye in the room after Whitehead finished speaking, spurring moderator and conference co-chair **Michael Blackton** to state: "This is the end result of our work, this is why it is important for us at PDA to collaborate together to bring these important drugs to market. This is the reason why we are here."

The next speaker (who had a tough act to follow!), **Thomas A. Leitch,** Vice President, Vector Manufacturing, bluebird bio, explored what the industry needs to do to ensure patients like Whitehead's daughter receive these therapies from the perspective of a major cell and gene therapy manufacturer.

"When I hear Tom share that amazing story, I cannot help but think what amazing times we are living in…right now there are approved cell and gene therapies that are helping transform lives," he said. "But there is a catch…for these therapies to realize their full potential, we are going to have to find new ways to supply them in volumes greater than anything we have ever seen before."

This requires transforming current manufacturing processes to enable manufacturing and supplying personalized batches, often within very short timeframes. This scaling challenge, Leitch emphasized, is the biggest hurdle to commercializing these lifesaving products. He cited the example of a personalized chimeric antigen receptor (CAR) T-cell therapy that requires, at a minimum, 80 staff for ten to 14 days of batch processing. That is for just one patient. The challenge occurs when that is expanded out to 10,000 patients with 400 batches ongoing at a given time. This requires almost *eight million pages of documents!*

"If complexity is the opposite of compliance, those numbers are going to be hard to sustain," Leitch said.

In bluebird's case, for one such therapy, the company turned to a contract manufacturing organization (CMO) that had the capacity to produce a clinical batch right then and there. Following a positive outcome from this initial batch, the trial expanded, necessitating a second CMO. In preparation for commercial launch, bluebird began building its own suspension platform. As the company neared launch, bluebird brought in a third CMO but continued to build out the suspension platform in tandem. In addition, the company planned to build its own manufacturing facility.

The next session delved further into the topic of facility design. **John R. Dougherty,** Lead Process Engineer, DPS Group, explained how his firm designed a flexible gene therapy manufacturing site using a process-centered design. He explained that a "flexible" facility can mean different things to different manufacturers, from the capability to process multiple types of products to the ability to support both clinical and commercial batches. The second speaker in the session, **Francesca McBride,** Director, Regulatory Compliance, Jacobs, outlined the cGMP considerations for cell therapy facilities, specifically citing limited materials available for lot release testing, fast turnaround when it comes to administration ➤

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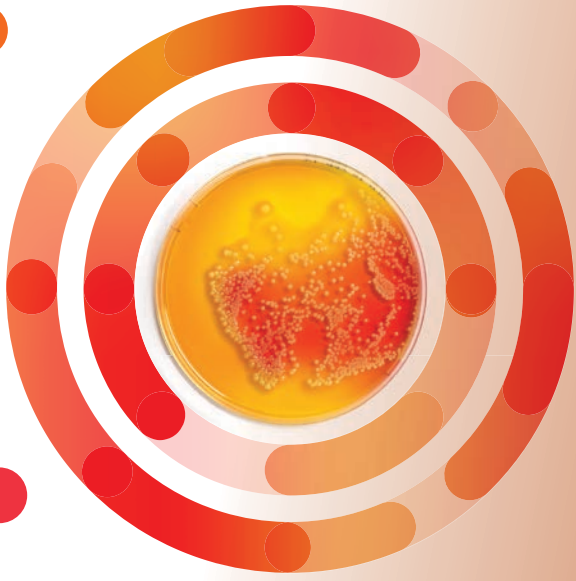

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> **But there is a catch…for these therapies to realize their full potential, we are going to have to find new ways to supply them**

and tracking to ensure patient-specific lots are delivered to the correct patient. Her presentation showed that designing a facility for cell therapies requires a risk-based approach to address these concerns.

EU, U.S. Regs Target CGTs

After lunch, the next two speakers reviewed regulatory requirements. For a Qualified Person (QP) perspective, QP **Stephanie Verbrugghe,** CEO and Founder, Farbridge Pharma Consulting, presented, "Launching Clinical Trials in Europe." European regulatory requirements in this area fall under the EudraLex clinical trial guidelines. Manufacturing of cell and gene therapies (referred to as "advanced therapy medicinal products") must comply with GMP guidelines geared specifically for this class of product. Batches imported into the European Union must have a manufacturing and importation authorization (MIA). The QP must audit non-EU manufacturers and QC labs and provide a declaration to the relevant regulatory body.

Steven Oh, PhD, Deputy Director, Division of Cellular and Gene Therapies, Office of Tissue and Advanced Therapies, CBER, U.S. FDA, then provided an FDA perspective on product lifecycle and CMC issues. First, when it comes to autologous products (i.e., products taken from a patient and then administered to the same patient) and allogeneic products (i.e., products with cells taken from one patient and delivered to others), there are common concerns around material qualification, establishing specifications, manufacturing facilities, manufacturing changes, supply chains, etc. For autologous products, specific challenges are product tracking and segregation, variability, limited material for testing, etc. and challenges for allogeneic products include donor eligibility, cell bank qualification, reproducibility of cell banks, scale up, etc.

In the face of these challenges, product characterization is critical.

"Product characterization should occur throughout the lifecycle, but it is expected that investment is made at the early stage of product development as this becomes very important as you start making manufacturing changes," Oh said.

The last session of the first day delved into the product characterization process. **Brendan G. Keenan,** PhD, Associate Director Quality Control Sciences and Technology, bluebird bio, started off the session with a look at analytical methods.

"There's still the expectation that any methods supporting your proprietary material would be validated," he explained, regardless of whether the product is a traditional biologic or a cell and gene therapy.

After Keenan's presentation, **Tam Soden,** PhD, Senior Director and Head of Analytical Development, Kite, reviewed analytical characterization for patient materials, highlighting potency method development in particular. She compared the process to Beethoven's 7th symphony, which weaves together both deep and light music in one piece.

CGT Companies Build Their Toolbox

Day 2 of the conference began with a look at applying quality risk management (QRM) principles to cell and gene therapies. For the first talk, **Marsha Steed,** Director Global QC Microbiology and Contamination Control, bluebird bio, covered microbial risk assessments for cell and gene therapies. She pointed to the recent EU Annex 1 revision that outlines use of QRM principles in manufacturing. At bluebird, the company relies on a tool called Hazard Analysis and Critical Control Point (HACCP). Steed recognized that companies may prefer to use different tools but emphasized the importance of "doing it well as patients need us to."

HACCP is a globally recognized solution for reducing hazard risk, originating in World War II and developed by Pillsbury for the U.S. space program. Since the 1970s, FDA has mandated that the food industry use HACCP following botulism cases due to improperly canned foods. HACCP is a qualitative risk assessment technique that "is a systematic, preventive approach to identify hazards in a process and/or system with the aim to produce a documented plan to control these hazards." The tool uses risk ranking and analysis and requires a hazard analysis and determining critical control points, which are then monitored extensively.

Michael Long, PhD, Senior Director Consulting Services, ValSource, then covered a similar risk assessment tool, the Interventions Risk Evaluation Model (IREM). This tool ranks the risk of interventions serves as a kicking off point. The IREM was showcased in the *PDA Letter* in 2016 ***(1).***

The next two sessions looked at raw material selection and control and supply chain challenges. All of these sessions emphasized that while there are significant raw material and supply chain challenges within the growing cell and gene therapy market, there are tools available to help address them.

At the close of the conference, Blackton referred back to Whitehead's power talk.

"Everything we do here results into some outcome for the patient," he said. "What we are doing is going to translate to people having better lives."

Reference

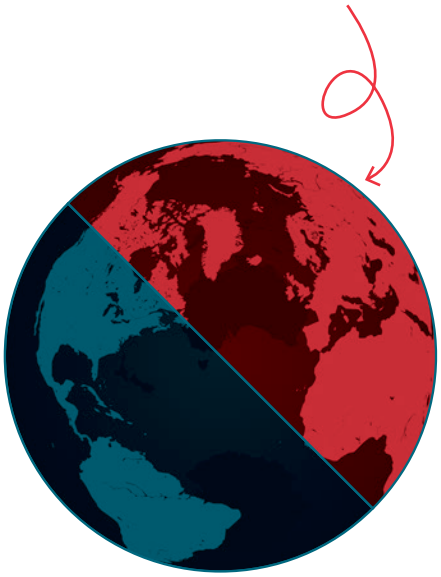
1. Baseman, H., et al. "A Line of Sight Approach for Assessing Aseptic Processing Risk: Part I." *PDA Letter* 52 (June 2016) 22-29.

Process Approach Goes Global

Earlier this year, the European arm of PDA's Quality Systems Interest Group surveyed members of its process owner subgroup about how they have implemented the process approach at their companies. While some of those surveyed began using a process approach ten years ago, others have only just started. Either way, there is strong support for the process approach in the industry as indicated by the results.

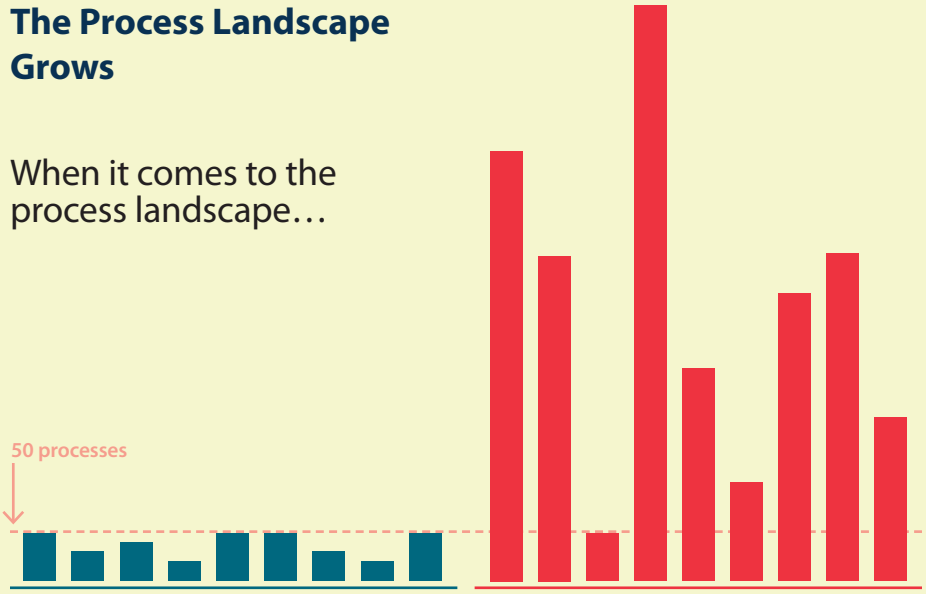
19 responded to the survey, 18 from pharmaceutical firms.

Half of those surveyed have used a process approach for more than three years.



The Process Landscape Grows

When it comes to the process landscape…



half of the companies have under 50 processes mapped while the other **half have mapped between 50 and 600 processes!**

Next Steps

This survey also indicated that there is a need for process owners with leadership skills and resources to effectively manage global processes.

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PUPSIT and the Annex 1 Revision

An Update on PDA's Activities Related to PUPSIT and the Draft Annex 1 Revision

Tina Morris, PDA, Maik Jornitz, G-Con, Gabriele Gori, GSK, and Hal Baseman, ValSource

In Dec. 2017, PDA and the Biophorum Operations Group began a collaborative effort to address industry and regulatory concerns related to preuse, post-sterilization integrity testing (PUPSIT) of filters used for sterilization of biopharmaceutical products. The objective of this collaboration is to provide industry and regulators with data to make informed decisions regarding suitable contamination control strategies to minimize the risk of contaminants entering the manufacturing process as a result of sterilizing grade filter failures.

Since 1998, the EU Guidelines to Good Manufacturing Practice: Medicinal Products for Human and Veterinary Use, Annex 1 (Manufacture of Sterile Medicinal Products), commonly referred to as "Annex 1," has contained the requirement for verifying the integrity of a sterilized filter before use and after its sterilization.

What is PUPSIT?

PUPSIT is an integrity test of a sterilizing grade filter before it is used but after it has been sterilized either by steam or gamma irradiation.

Why Use PUPSIT?

Concerns have been raised that a sterilizing filter could develop flaws that allow microbiological contamination to pass through during filtration. These flaws may then be blocked by fluid contaminants or components during the filtration process and remain undiscovered during the post-use integrity test. This phenomenon is referred to as filter flaw masking.

Why Not Use PUPSIT?

To test a filter that has been sterilized by current means, the sterile filtrate side of the sterilized filter must be under atmospheric pressure. The procedure for doing so results in a more complex process, stress on the sterilized filter and aseptic manipulations which pose a risk to product sterility.

Possible Risks of Filter Flaw Masking

For masking to occur, filter flaws must be small enough to avoid discovery during initial testing and to be closed by clogging. These flaws must also be able to grow large enough to pass microbiological contamination after sterilization, and, additionally, the product being filtered must have the ability to clog the filter.

Risk-Based Arguments for Not Using PUPSIT

(1) Filter flaw risks are low, due to control of filter manufacturing, handling and use; the risk is further lowered by presterilization filter integrity testing. The flaw masking risk is also low and depends on specific product characteristics.

(2) PUPSIT is a complex process, requiring additional manipulations of a sterilized system that elevate the risk of errors during routine operations.

(3) There is insufficient scientific evidence that masking of flaws can or does occur in commercial product filtration.

Risk-Based Counter Arguments to the Above Position

(1) There is a risk that filter flaws could be masked because filter manufacturing, transport and use are not sufficiently controlled and presterilization integrity testing is not universally performed.

(2) PUPSIT is not complex and does not increase the risk of system contamination. Industry PUPSIT risk assessments have been biased with predetermined outcomes. ➤

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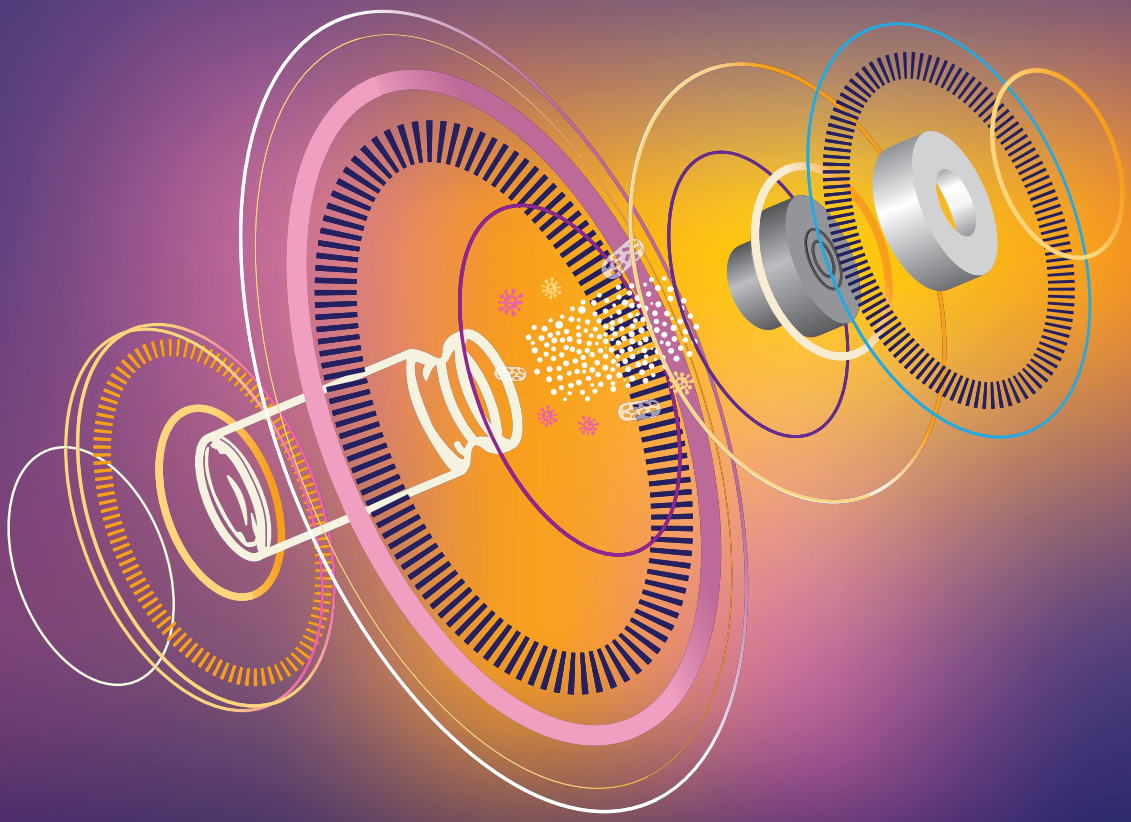

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Masking of flawed filters resulting in passed post-use integrity tests can occur under extreme conditions

(3) There is a lack of scientific evidence and data to show that blinding cannot or does not occur.

Taking into consideration these two different positions on PUPSIT, the following paradigms formed the basis of the PDA/Biophorum collaborative effort:

1. The effort must consider the opinions and concerns of industry and regulators on both sides of the debate.
2. There is a need for unbiased, objective, risk-based, scientific data and evidence.
3. PUPSIT is not a process or an objective. It is a test intended to reduce risk associated with aseptic processing and sterilization of biopharmaceutical product.
4. Ineffective efforts to reduce risk may be harmful in that they divert resources from efforts that can be more effective.
5. Prevention of a failure is a more effective risk mitigator than detection of a failure.

Project Status and Update

The collaboration workstream deliverables are designed to provide industry with guidance to determine if processes and products pose a risk of masking, and, if so, how best to prevent the occurrence of failure. This approach encourages application of QRM principles focused on prevention of those conditions that might result in flaws and masking rather than just detection.

Workstream 1 – Masking Study

Description: Nonintegral filters were challenged with a biological fluid of foulant concentrations at various blocking rates. The objective of the first phase of the study is to see if masking could be replicated using a foulant concentration fluid and blockage rate well beyond commercially feasible conditions. The second phase of the study included experiments at foulant concentrations and foulant rates closer to upper edge commercial conditions to determine which conditions favor masking and which do not pose a risk of filter masking.

Status: The first part of the study has been completed successfully at PDA's Training and Research Institute in Bethesda, Md. using flawed filter cartridges. It is important to note that to replicate the masking effect, the concentrations of organic materials needed to be increased to a level well above any what would be attempted, encountered, or practical in commercial pharmaceutical manufacturing. The next steps included repeating experiments at conditions similar to commercial usage, using flawed cartridge filters and laser drilled disc filters. The goal is to submit the study and data in combination with other findings to the *PDA Journal of Pharmaceutical Science and Technology* for publication and peer review.

Discussion: Masking of flawed filters resulting in passed post-use integrity tests can occur under extreme conditions. Tests performed using lower foulant concentration to better simulate real commercial manufacturing operations showed that the flawed filters at a various blocking rates were detected as flawed by the post-use integrity test. This may indicate that masking of flawed filters under most commercial conditions would not occur. The results must be evaluated in combination with other workstream results, as well as the correlation between laboratory produced flaws and commercially occurring flaws.

Workstream 2 – Data Mining

Discussion: The data mining effort is an analysis of historical data from standard bacterial challenge tests of 0.2µ and 0.45µ filters generated for a variety of products as part of filtration ➤

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PDA lives its motto – Connecting People, Science, and Regulation® – every day through our engagement with health authorities and pharmacopeias around the world. In harmony with our consensus-driven, peer-reviewed Technical Reports, PDA members collaborate in Commenting Teams to develop responses to draft regulations and guidances that reflect our vision of maximizing product quality, availability, and value.

- We advocate for global harmonization, simplification, and efficiency in the regulations that impact the manufacturing science of pharmaceuticals, biopharmaceuticals, and advanced therapies. Harmonization of regulatory requirements—in both text and application—can drive innovation, quality performance, and compliance.
- We help guide regulators on emerging science and technology topics. As the industry continues to shift from traditional pharmaceuticals and biologics to novel therapies, and as manufacturing technology advances, PDA can identify and help health authorities resolve real-world implementation questions before they impact patients.

PDA is uniquely positioned to help regulators create workable and innovative regulatory solutions that protect product quality and availability. With more than 10,500 members and 26 chapters globally, PDA can gather diverse perspectives on regulatory initiatives, and can connect regulators and experts on topics that impact manufacturing science. PDA succeeds because of the hard work, determination, and diversity of its volunteers and members.

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Companies and Regulators should use a nonbiased, risk-based approach

process validation studies. The objective is to understand the propensity of product fluids to increase the bubble point between pre- and post-testing and establish definitions of known and potential failure modes as well as conditions under which preuse failed filters may be masked.

Status: Initial data mining and analysis is complete. The results of the study and data in combination with masking study data will be submitted to the *PDA Journal of Pharmaceutical Technology* for peer-reviewed publication.

Discussion: The data mining showed that a pre- and post-use bubble point value shift is extremely rare. The entire dataset is currently undergoing additional statistical analysis, including review of the outliers found and potential reasons for them.

Workstream 3 – FTA (Fault Tree Analysis) Risk Assessments

Discussion: Risk assessments were performed by filter manufacturers and filter users on filter manufacturing, transport, handling and use. The FTA identified failure modes, evaluated the effectiveness of control measures, and, where needed, identified control measures to reduce risk of failure. The objective is to provide guidance to help filter manufacturers and users define a robust quality risk management (QRM) approach to determine risks of sterile filter failure and define a robust control strategy based on scientific understanding and the associated risk.

An expanded version of this article is available on the PDA letter website www.pda.org/letter

Status: The FTAs have been completed. It is anticipated that example FTAs will be published and made available to the industry as part of an overall report or points to consider in combination with other deliverables.

Discussion: A sound, comprehensive risk assessment, specific for each process and product characteristics can be a key part of the development of an effective contamination control strategy. With failure modes identified, the FTA can be used to help filter manufacturers and users determine, implement and evaluate controls to reduce the risk of filter flaws. These assessments will help inform risk identification and analysis for those instances in which specific detection controls, such as PUPSIT, are necessary for inclusion in the overall filtration control strategy.

Workstream 4 – PUPSIT Best Practice Points to Consider

Discussion: The objective is to prepare a comprehensive guide for the selection, design and use of PUPSIT under varying circumstances, incorporating information from a PUPSIT FMEA risk assessment.

Status: The Points to Consider and FMEA have been completed and are under review for PDA publication.

Discussion: The best practice guide should make the reader aware of the care, control and training required to design, install and maintain a proper PUPSIT system and successfully control and perform the PUPSIT process. Design and operation must take into consideration the potential risk posed by exposure of the downstream filter assembly to the atmosphere, the additional risk of component malfunction or improper operation, the increased interventions and activities occurring in the aseptic area and stress placed on the sterilized filter during spot sterilization testing. This effort also makes clear there are a multitude of complexities which must be further evaluated, including drying pressures and time for water wetted filters and other adverse effects for product wetted filters, as well as the risk of damaging the filter if the sterilization process is not controlled per the filter manufacturer's recommendations.

Ancillary Research

As the development of the workstreams progressed, it became apparent there was a need for additional research. To that end, two surveys were conducted, one on loss of product sterility as a result of PUPSIT performance and another on efforts required to plan and implement PUPSIT

Conclusion

It is important to wait for all workstream activities to be completed, results analyzed, reviewed and compared to other supporting workstream results and analysis before drawing and stating conclusions. The team, however, is certain of the following:

1. Companies and regulators should use a nonbiased, risk-based approach drawing on scientific evidence from objective data to make decisions on the feasibility and validity of controls to prevent aseptic process failures.

2. Where little or no scientific evidence or data is available, that should be a signal to industry and regulators to obtain or develop that evidence. Where the evidence supports or promotes prescribed or alternative approaches that are beneficial and suitable for the process/product in scope, those approaches should be considered and adopted.

3. Where evidence is presented, results published and positions offered, the team involved in this collaboration encourages and welcomes commentary and discussion from industry, suppliers and regulators on how to best interpret and communicate these results.

4. More to come…

Suggestions for FDA Voluntary Recalls Doc

24 June 2019

Mr. Peter Fox
Office of Regulatory Affairs
Food and Drug Administration
12420 Parklawn Dr. Rm. 4146
Rockville MD 20857

Re: Initiation of Voluntary Recalls Under 21 CFR part 7, subpart C; Draft Guidance for Industry and FDA Staff (Docket No. FDA-2018-D-2074)

Dear Mr. Fox:

PDA appreciates the opportunity to comment on FDA's Draft Guidance for Industry and Staff regarding Initiation of Voluntary Recalls Under 21 CFR part 7, subpart C. In general, the draft guidance provides useful information. In our attached comments, PDA offers specific suggestions that may provide clarity for agency staff and regulated industry.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments have been prepared by a committee of volunteers with expertise in pharmaceutical and biopharmaceutical manufacturing on behalf of PDA's Regulatory Affairs and Quality Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me via email at johnson@pda.org.

Sincerely,
Richard Johnson
President and CEO
cc: Tina Morris, PDA; Ruth Miller, PDA

PDA Commenting Task Force

Karin Baer, Boehringer Ingelheim

Cheryl Roeland, Emergent BioSolutions

Can We Reprogram the Human Computer? continued from page 28

"I actually see this giant barrier to entry of regulation naturally reducing when you can do more directed development that actually can be understood in a simulated model."

As far as the future, Galvin sees limitless possibilities for his company.

"What I tell my people is 'that is great you solved HIV, now find a better solution because if we do not obsolete ourselves somebody else will certainly do it.' That is what I carry from the software world," he says. "Visicalc was the dominant spreadsheet… and Lotus 123 wiped them out. Now, Excel wiped out Lotus 123. If you do not innovate in high-tech, you are dead. High tech has come to drug development."

He also expects to continue drawing on his experiences in Silicon Valley. When he talks, you can almost imagine him launching a biotech product like Steve Jobs launched the iPhone at one of Apple's annual, eagerly anticipated product launches in 2007.

"I want to solve HIV. I want to solve a whole slew of infectious diseases. And I want to solve cancer," Galvin emphasizes. "I will tell you. I had the same level of excitement when I worked at Apple. This is the first time I have seen another 'Apple-level' of opportunity excitement and disruption."

Did you like this profile? We are looking for recommendations for thought leaders we could profile in future issues.

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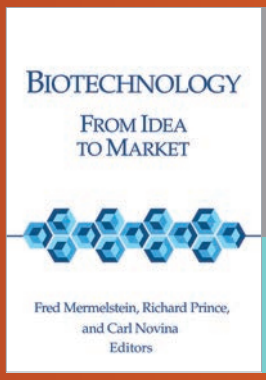

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Editors: Fred Mermelstein, Richard Prince, Carl Novina

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Incorporating QRM into Cell and Gene Therapy Processes

Lori Richter, ValSource, and Ghada Haddad, Merck

The principles of quality risk management (QRM) are certainly not new with ICH Q9: *Quality Risk Management* and ISO 14971 Medical Devices—Application of Risk Management to Medical Devices being present in the industry for quite some time now. But do these concepts pose unique challenges for implementing QRM within the cell and gene therapy space?

Cell and gene therapy processes can differ from traditional manufacturing. This may result in a variety of challenges when integrating QRM methodologies into decision-making. Current manufacturing technologies require human interventions which inherently introduce risk.

These issues and more will be discussed at the inaugural *2019 PDA Quality Week*. The theme of this conference series is "Mastering Risk Management for Organizational Success," and the series will focus on various aspects related to QRM.

The first meeting for the week is titled *Risk Management in the Regulatory Landscape* and is scheduled for Dec. 9–10. This phase will provide participants with background on QRM. The second phase of this conference week is a workshop scheduled for Dec. 11, *Building a Foundation and Culture for Quality Risk Management Integration.* This workshop will focus on the basic foundational elements needed to incorporate risk management thinking into the company culture throughout the organization. The final phase of this conference series is *Optimizing Quality Risk Management* and it will give attendees the necessary tools and concepts to help them implement and sustain a successful QRM program. During this session **Monica Hueg,** Managing Consultant, NNE Denmark, and **Tais Conti,** Quality and Compliance Department Manager, Bristol-Myers Squibb Company, have been invited to speak on the topic of executing QRM in advanced cell and gene therapy biologics.

Join us for an opportunity to get into some in-depth and insightful conversations regarding QRM in the biopharmaceutical industry!

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Exciting Times Bring Challenging Paradigms

Melissa Seymour, Biogen

We are living in exciting times. Medicine and pharmaceuticals are advancing at a rate never before seen. Personalized medicine is changing the way doctors interact with patients by tailoring specific treatment regimens to the individual. RNA-based therapeutics seek to "interfere" with genes at the RNA level and stop abnormality in genes before it happens. Cell and gene therapies are becoming a reality and the global world is becoming smaller and smaller. We live in exciting times where the challenge of "keeping up" is paramount to ensuring we provide the best options and treatments for patients.

PDA is helping alleviate these challenges by providing resources on emerging technologies in order to advance pharmaceutical and biopharmaceutical manufacturing.

PDA is particularly active in the biopharmaceutical and biotechnology arena. Here, treatments use living cells or genetic material to treat conditions. PDA Europe introduced its inaugural *BioManufacturing* conference in Munich last month. Next year, we will continue our focus on advanced therapy medicinal products (ATMPs) at the PDA Europe conference on the topic in Brussels, June 24–25. This has been a particularly successful meeting, bringing together industry, academia and regulators to discuss the many challenges with ATMPs from raw materials to technology transfer to testing to registration.

Manufacturing science continues to advance at unprecedented rates with artificial intelligence, machine learning and complex biological datasets requiring new and advanced ways of thinking. Informatics and data science are driving approaches that will inevitably become part of day-to-day operations, in particular, approaches relating to manufacturing, data management, the supply chain and distribution as well as the ultimate patient experience. PDA is also helping to create awareness and understanding around these issues. In fact, this month, we will host the workshop, *Innovating the Journey from Manufacturing to the Patient,* Oct. 21, in Gothenberg, Sweden.

Of course, all these advancements provide additional complexity as global regulators must ensure safety for patients while, at the same time, allowing innovation to progress for new and exciting therapies that could change the way we treat many of today's most troubling diseases. PDA has long been committed to promoting collaboration between regulators and industry in order to advance pharmaceutical manufacturing. As such, PDA once again hosted the *PDA/FDA Joint Regulatory Conference* in Washington, D.C. last month. Working with regulators on key topics around ATMPs, serialization, advanced virus technologies and more is critical in ensuring we all work together to achieve the most comprehensive and compliant path forward.

While the future may be a bit scary and the rate of change appears staggering, if we work together to define solutions, we can provide value by connecting people, science and regulation®.

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