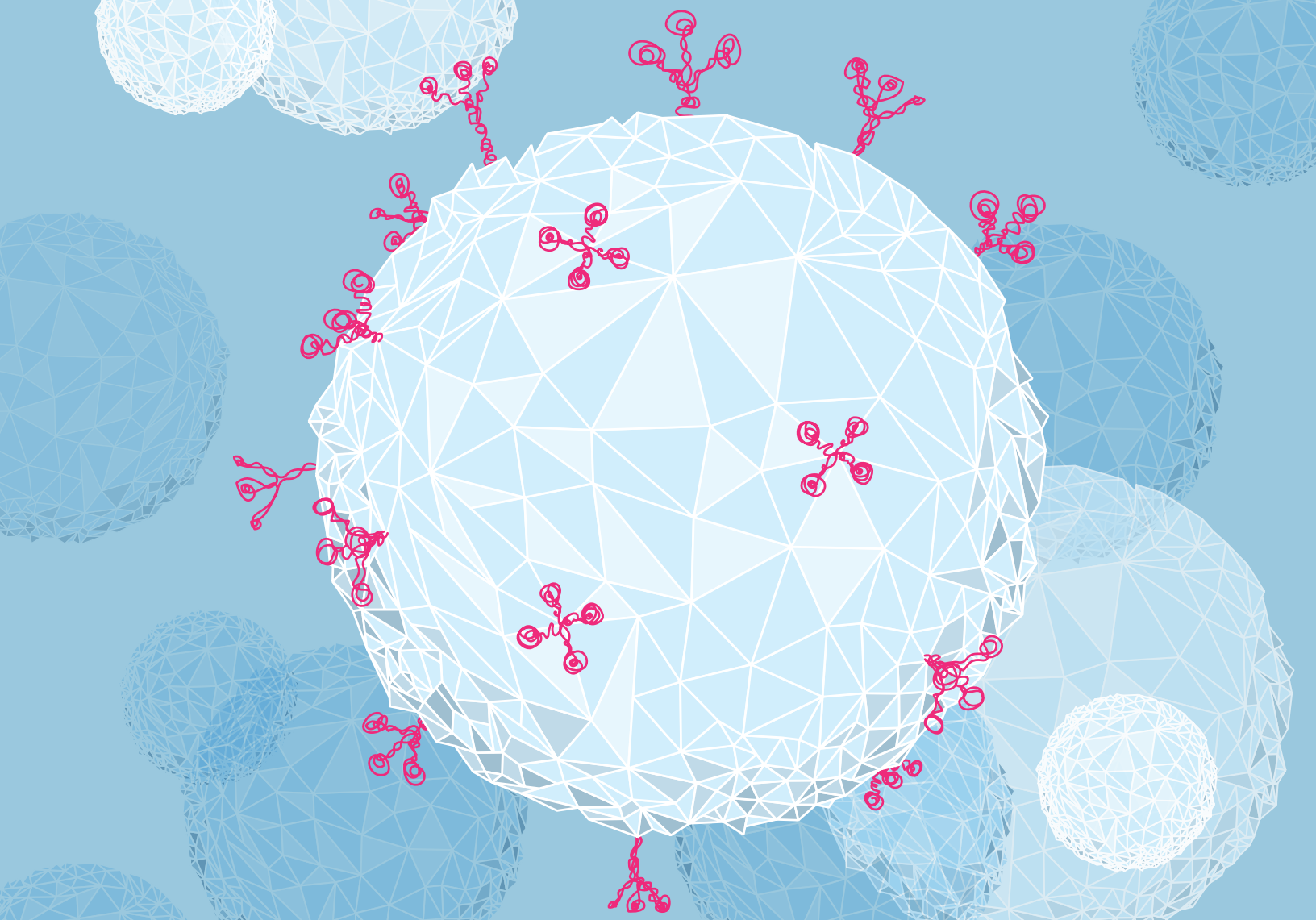
People • Science • Regulation

PDA Letter

Volume LIV • Issue 4 www.pda.org/pdaletter April 2018



New Therapies Need Novel Take on Manufacturing

PDA®
Parenteral Drug Association

PDA: The Recognized Leader in Aseptic Processing Tools and Resources

For more than 70 years, PDA has been recognized worldwide as a leader in the definition and improvement of sterile manufacturing. With the advent of new biological therapies, the importance of proper aseptic processing has never been greater.

With up-to-date technical information, world-class training, international conferences and workshops, and benchmarking surveys, PDA is the "go-to" resource for all your aseptic processing needs!

Our multi-faceted, global cooperative efforts have resulted in initiatives to assist and advance the industry, including:

- Development of best practices
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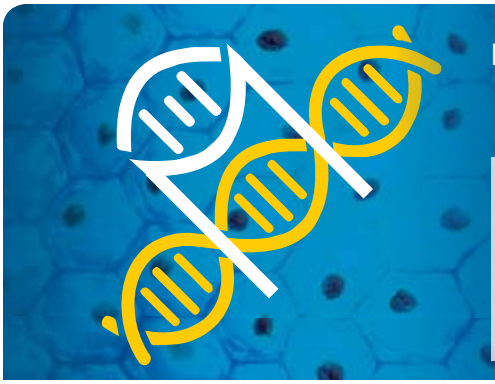
- Advancement of science-based solutions to technical challenges

When you are in need of aseptic processing tools and resources, turn to PDA!

To learn more about how PDA is promoting progress in aseptic manufacturing, visit www.pda.org

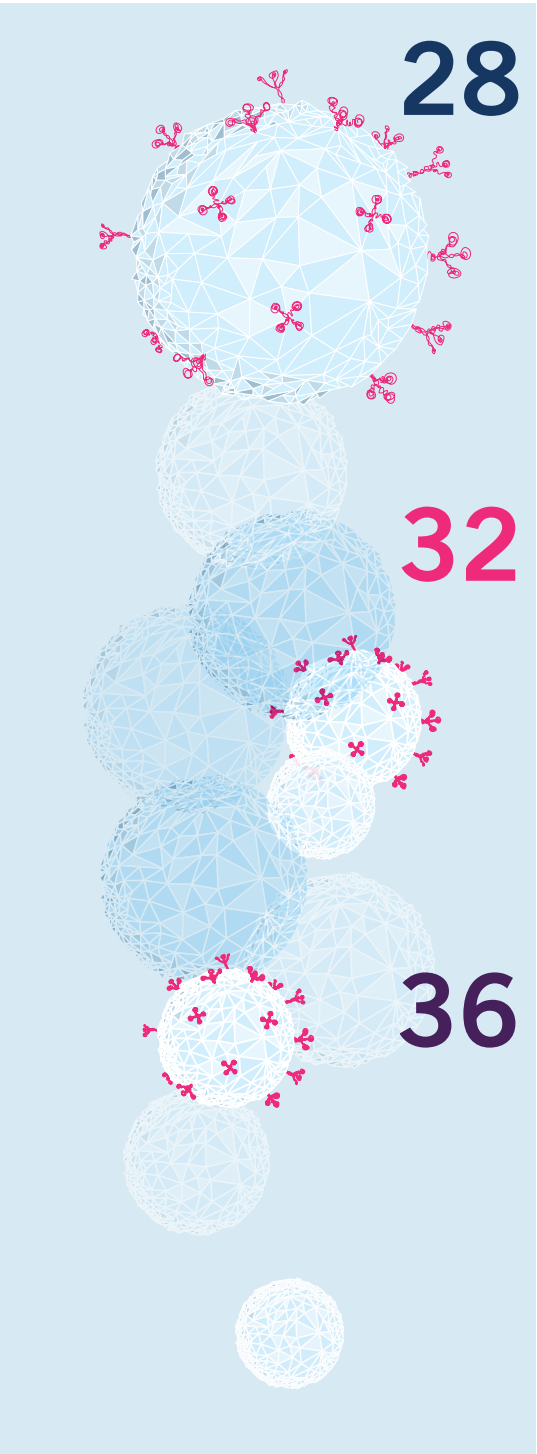
April 2018 PDA Letter



PDA Europe Conference on Advanced Therapy Medicinal Products

Show Issue

This year's *Advanced Therapy Medicinal Products* conference takes place in the city of Amsterdam, June 5–6. Articles with this banner at the top of the page include information relevant to this meeting and these innovative new therapies.



Cover Art Illustrated by Kaija Yount

Speaking the Language of GMP

An interview with Dr. Lutz Uharek

Rebecca Stauffer, PDA

How can clinicians involved with cell therapies learn the language of GMP? This year's Chair of the *Advanced Therapy Medicinal Products* conference, **Lutz Uharek,** speaks to the *PDA Letter* about his experience moving from the clinic to a GMP environment.

Cell and Gene Therapies Present Challenges, Promise

Joshua Eaton, PDA

Did you miss last year's PDA *Cell and Gene Therapy Conference*? This summary offers a look at the main topics of discussion at the conference,including, talks from regulators.

InfoGraphic

Cell and Gene Therapies By the Numbers

A look at the current and future state of cell and gene therapies.

PDA Letter

Volume LIV • Issue 4 www.pda.org/pdaletter

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Subscriptions are not available.

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Digital Exclusives

> **On the Issue | USP <660> Containers-Glass**
Corning's Timothy Hunt discusses planned revisions the USP chapter <660> Containers-Glass.

> **Novel Manufacturing Tech Drives Novel Product Development**
Read a summary of some of the manufacturing sessions at last year's *Universe of Pre-filled Syringes and Injection Devices.*

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Pharmaceutical and Biopharmaceutical Manufacturing: Understanding Your Process Series

The U.S. FDA plans to take a risk-based approach to biomanufacturing inspection and changes are expected very soon. With regulatory expectations and the impending changes anticipated in 21CFR 600 in June 2018, now is the time to get up to date on managing risk to safely produce healthcare products!

In order to help you, we have gathered chapters from our most successful risk-based texts. These convenient, electronic texts define risk, discuss hazards and risks, provide tools to help you evaluate risk, and develop effective strategies for dealing with risk.

Written by subject matter experts, each text contains practical applications, an extensive list of international regulations for reference, and suggested PDA Technical Reports and books for further guidance.

- **Risk Management Library, Volume 1: Lifecycle Risk Management**
  Editors: Edwin Bills and Stan Mastrangelo
  Item No. 18044
- **Risk Management Library, Volume 2: Practical Approaches to Risk-Based Compliance**
  Author: Siegfried Schmitt
  Item No. 18045
- **Risk Management Library, Volume 3: Practical Approaches to Risk Assessment and Management**
  Author: James L. Vesper
  Item No. 18046
- **Risk Management Library, Volume 4: Practical Approaches to Risk Assessment and Management Problem Solving**
  Author: Tim Sandle
  Item No. 18047
- **Risk Management Library, Volume 5: Risk Problem Solvers: Failure to Follow Established Procedures**
  Editors: Russell E. Madsen and Maik W. Jornitz
  Item No. 18048
- **Risk Management Library, Volume 6: Risk Problem Solvers: Lack of Process Understanding**
  Editors: Russell E. Madsen and Maik W. Jornitz
  Item No. 18049
- **Risk Management Library, Volume 7: Risk Problem Solvers: Inadequate Facilities, Procedures and Process Control**
  Editors: Russell E. Madsen and Maik W. Jornitz
  Item No. 18050

Price for each Series: PDA Member $100 | Non-Member $125

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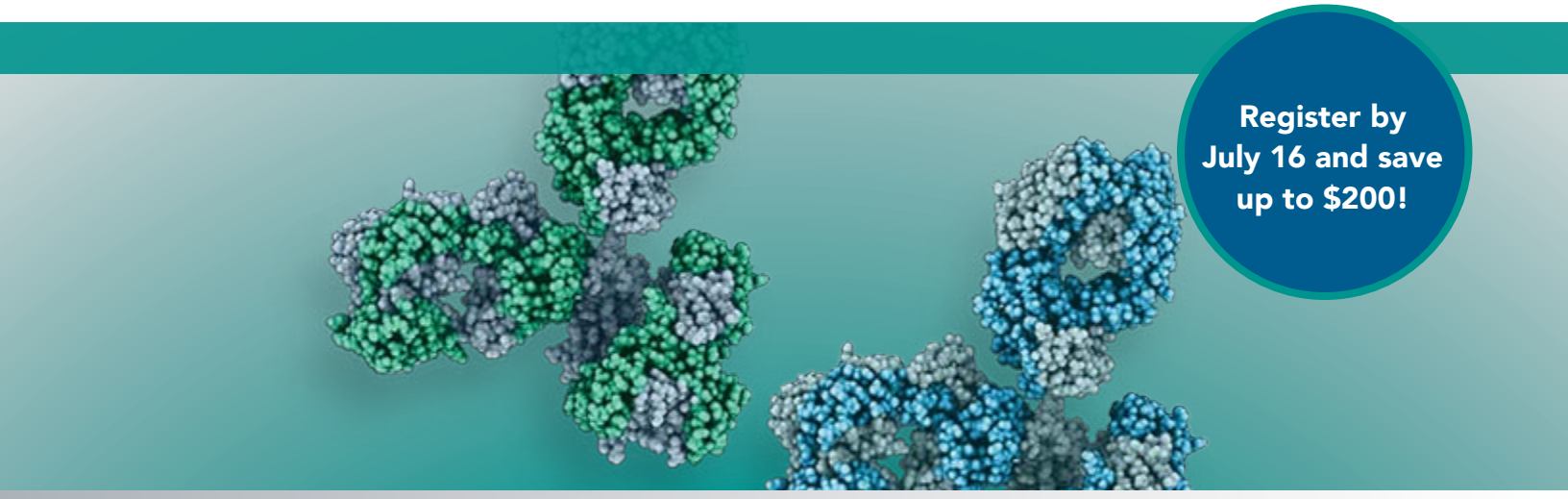
2018 PDA Biosimilars Workshop



Register by July 16 and save up to $200!

The *2018 PDA Biosimilars Workshop* will bring together industry experts and regulators to discuss and highlight the strategies required to successfully bring biosimilars to market.

Speakers from various health authorities will provide their experience and views on key aspects for a biosimilar development program, setting the framework for what should be included in a marketing application.

Other Workshop sessions will address important topics, such as:

- Analytical similarity testing – statistics and methodology
- Compliance standards for analytical similarity data
- Expectations for manufacturing
- The role of devices and container closure systems
- Suitable reference standard lifecycle program
- Method validation strategies
- Globalization of biosimilars programs, complexity of supply chains

Benefit from case studies and practical examples illustrating how analytical similarity can be demonstrated and practical control strategies can be developed and hear current updates from the regulatory agencies. CMC reviewer perspectives will elucidate CMC issues that have been most challenging for review of 351(k) BLA applications.

Learn more and register at pda.org/2018Biosimilars

PDA® Parenteral Drug Association

September 26-27, 2018 | Washington, DC
Exhibition: September 26-27
#PDABIOSIMILARS

CONNECTING PEOPLE SCIENCE+ REGULATION®

Novel Meds Come into Their Own

Last year was a big year for cell and gene therapies, and I am sure that 2018 will be a bigger year for these products as well.

Last summer, the U.S. FDA approved the first U.S. gene therapy product in Novartis' Kymriah. This product treats patients with acute lymphoblastic leukemia, and is primarily aimed at younger patients up to 25 years of age. Kymriah uses a patients own T cells to fight cancer cells. Since then, FDA has approved further gene therapy products, including Spark Therapeutics' Luxturna, a gene therapy that treats an inherited blindness condition. Luxturna is the first FDA-approved gene therapy that targets a disease caused by mutations in a specific gene.

Rebecca Stauffer

Prior to the approval of Kymriah, the *PDA Letter* team was fortunate to film **Karen Walker,** who oversaw the manufacturing aspects of Kymriah, at last year's *PDA Annual Meeting* in Anaheim, Calif. for an "On the Issue" video (https://youtu.be/qqmQ8S-LOyWk). With this in mind, I was grateful to have the opportunity to see Karen at this year's Annual Meeting in Orlando, Fla. Karen moderated a session on the unique supply chain challenges facing personalized medicine products. **Kirstin Powel** showed how Novartis uses an integrated manufacturing and supply chain platform which reduces the turnaround time for Kymriah to just 22 days.

Karen Walker discusses how Novartis overcame manufacturing challenges for Kymriah in an "On the Issue" video

Suzanne Farid, PhD, a professor of biochemical engineering with the University College London, closed out the session with a presentation on her work with developing decision support tools to help companies determine the best strategies for manufacturing an allogenic cell therapy.

This exciting information shows how the industry is dealing with challenging manufacturing processes and supply chains for cell and gene therapies. PDA is also doing its part. In addition to the Annual Meeting session mentioned above, PDA will hold its tenth *Advanced Therapy Medicinal Products* conference in early June in the scenic city of Amsterdam. PDA will also be hosting a *Cell and Gene Therapy Conference* in October in Bethesda, Md. PDA recently announced its new Interest Group for these products, and a Task Force is working hard to complete PDA's first Technical Report in this field.

No doubt, there will be more cell and gene therapies approved in the coming years. PDA will continue to address the issues around manufacturing these innovative therapies in the Letter, the *PDA Journal of Pharmaceutical Science and Technology,* technical reports, training courses and conferences/workshops.

Correction

On page 14 of the March issue the photos of **Jennie Allewell** and **Nikki Mehringer** were mislabeled. Jennie Allewell is depicted on the left and Nikki Mehringer is depicted on the right.

Announcing the *PDA Letter* Article of the Year

PDA and the editors of the *PDA Letter* have launched the Article of the Year recognition. Congratulations go to **Frithjof Holtz** of Merck KGaA, Darmstadt, Germany. His January 2017 article, "Formalizing a Risk Assessment for Excipients," is the *PDA Letter* Article of the Year for 2017. The article is currently available on the *PDA Letter* website.

Holtz is working with PDA's Regulatory Affairs and Quality Advisory Board (RAQAB) on a joint technical report on risk assessments for excipients in partnership with IPEC.

Call for Nominations for 2019–2021Board

PDA's Nominating Committee seeks member recommendations for nominees of candidates to fulfill Board of Director positions for the 2019–2021 term. Nominees must be current PDA members in good standing. This year's committee is chaired by **Martin VanTrieste,** Immediate Past Chair of the Board of Directors.

If you are interested in being considered or want to recommend someone, send a recommendation (including full name, contact information and rationale for nomination) by email to nominate@pda.org or by regular mail to PDA Global Headquarters, Bethesda Towers, Suite 600, 4350 East West Highway, Bethesda, MD 20814, USA, Attention: Nominating Committee. Please include any supporting information that may make it easier for the Nominating Committee to evaluate your recommendation. Nominations are due May 15.

If you have any questions, feel free to contact PDA President **Richard Johnson** at johnson@pda.org or Martin VanTrieste at mvantrieste@gmail.com.

Global Pharmacopeial Reps to Speak in May

Representatives from pharmacopeias and regulatory agencies across the globe are scheduled to speak at the PDA Europe *Pharmacopoeia Conference* scheduled for May 29–30 in Vienna. PDA is honored to welcome speakers from the following pharmacopeias and agencies:

- European Directorate for the Quality of Medicines & Health-Care, EDQM (European Pharmacopoeia)
- U.S. Pharmacopeial Convention
- Japan Pharmaceuticals and Medical Devices Agency
- Russian Ministry of Health
- Eurasian Economic Union Pharmacopeia Committee
- Indian Pharmaceutical Commission
- Brazil Pharmacopeia
- Ghana FDA
- WHO (International Pharmacopoeia)
- MHRA
- British Pharmacopoeia Commission

To learn more and to register, visit www.pda.org/eu/pharma2018.

Check Out the New and Improved PDA Connect℠

On Feb. 19, PDA unveiled an updated version of PDA Connect℠, our online networking community, based on user feedback.

If you have not already, log in to PDA Connect℠ to explore new and improved features, such as:

- Mobile-friendly design
- Intuitive navigation
- Community-oriented layout
- Popular "newsfeed" format

You can access the updated version of PDA Connect℠ with the same login credentials you currently use to log into your PDA account. The site can be accessed at community.pda.org.

PDA Connect℠ provides a forum for PDA members around the world to share information, advice and best practices on a wide variety of important topics.

PDA Volunteer Spotlight

Sateesh Yelisetti

- **Quality Director- ECM & SQ, APAC**
- ***Baxter Healthcare (Asia) Pte Ltd***
- Member Since | **2013**
- Current City | **Singapore**
- Originally From | **Vijayawada, India**

Use a holistic approach to resolve any issue

What has been your most memorable PDA experience to date?

It was an honor to be part of the team responsible for organizing the first PDA Singapore Chapter event in 2016. I am now president of the chapter and look forward to organizing further chapter events to support the pharma community in Singapore.

What made you become a PDA volunteer?

I expanded my involvement with PDA because my work as a volunteer enhanced my professional knowledge of the field.

What significant changes have you seen take place in your area of expertise through the years?

Risk management has become an aspect in all major elements of parenteral manufacturing.

How has PDA contributed to your professional career?

It has increased my knowledge of regulations, increased my network within the pharma industry and helped me improve my technical writing.

What advice has helped you in your career?

I was advised to take risks, and this has led me to achieve great things.

Do you have a morning routine for success you would like to share?

Each morning I spend 15–20 minutes planning for the day ahead.

What do you like to do in your free time?

I like to give back and volunteer to help my community.

Tell us about a special skill you have.

I am really good at cooking Indian food.

PDA Regulatory and Compliance Course Series

During PDA's *Regulatory and Compliance Course Series*, learn about root cause investigations, implementing an effective GMP auditing program, and preparing and managing documents.

Course Offerings Include:

- *Root Cause Investigation for CAPA* | **May 1-2**
  In this course, you will be introduced to a seven-step investigation methodology to determine the root cause of a technical problem and get to put your new skills to the test by applying them to a case study based on real-life investigations!
- *Quality Metrics and Quality Culture* | **May 3**
  Examine your quality management system, select appropriate quality metrics that drive intended behaviors, and determine how best to collect and use the data to improve your quality systems using the ICH Q10 guidance as framework.
- *Preparing and Managing Documents and Documentation for Compliance – New Course* | **May 4**
  During this new course, you will examine U.S. FDA and EU regulatory requirements and expectations for GMP/GDP documents.

Learn more and register at pda.org/2018RCCS

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

PDA Parenteral Drug Association

May 1-4, 2018 | Bethesda, MD

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Volunteering Opens Doors for Student Chapter

Dahlim Kim and Jasmine Tat, Keck Graduate Institute

In December, we were given the opportunity to attend the *2017 PDA Cell and Gene Therapy Conference* as volunteers from the PDA Southern California Chapter's student chapter. Our duties included checking badges and collecting question cards at the end of each talk—the latter we found valuable for assisting the session facilitators to stimulate discussions. Additionally, this volunteer opportunity allowed us to attend the sessions alongside conference attendees, providing a unique opportunity to network with multiple industry professionals within the growing cell and gene therapy niche.

(l-r) Richard Johnson, Dahlim Kim, Jasmine Tat and Brooke Schneider

The conference was an amazing opportunity for us to learn about emerging technologies and the current challenges many companies are facing in the context of cell and gene therapy. As two Master's of Engineering students majoring in biopharmaceutical processing, we have been fortunate to be introduced to next generation cell and gene therapies through both faculty and guest lecturers within our educational program. This has included learning about manufacturing challenges of cell and gene therapies compared to the traditional monoclonal antibody (mAb) platforms, quality-by-design (QbD) principles and the developing regulatory landscape. Thanks to this background knowledge, we were extremely interested in the talks featured in this conference, covering a comprehensive range of topics from facility design elements for autologous treatments to the use of artificial intelligence to enhance drug target discovery. Additionally, the

conference opened our eyes to how smaller companies are using prior knowledge gained from larger companies' experiences with the mAb standard for manufacturing, QbD and facility design to piece together processes, risks and control strategies for these novel therapies.

this conference was a very positive experience that provided us a great base of technical knowledge

Another important part of our experience was meeting industry leaders from multiple facets of this industry, such as R&D, process development and quality. Over two days, we took advantage of the networking sessions to learn about others' experiences, what it is like to work in both large and small companies and the different jobs that people have moved through to get where they are today. Learning from people who have been in the industry for years is important for those of us who seek insight into what different professional specialties might hold for us. Altogether, this conference was a very positive experience that provided us a great base of technical knowledge in how companies are tackling challenges in the cell and gene therapy space with the added bonus of professional development.

We sincerely thank everyone at PDA for organizing a successful and educational event, as well as all the conference attendees and facilitators who shared their experiences with us, adding to our excitement about the emerging cell and gene therapies field. In addition, we would like to recognize the following individuals for giving us this once-in-a-lifetime opportunity: **Madelyn Low, Randy George, Richard Johnson** and **Brooke Schneider.** **[Editor's Note:** For a summary of the *2017 PDA Cell and Gene Therapy Conference,* see story on p. 32**.]**

PDA Who's Who

Randy George, Southern California PDA Chapter President

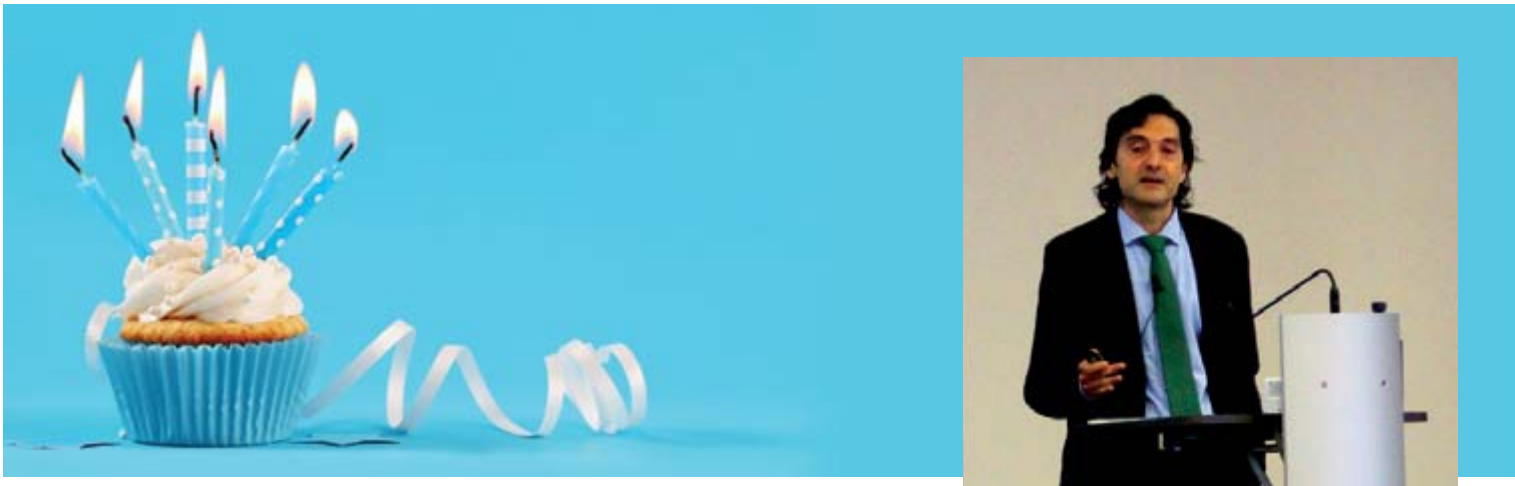
Richard Johnson, PDA President and CEO

Madelyn Low, PDA SoCal Student Chapter President

Brooke Schneider, Program Manager, PDA

PDA Celebrates Ten Years of ATMP Conferences

This year marks the tenth anniversary of PDA Europe's annual *Advanced Therapy Medicinal Products* conference. To celebrate, there will be a special event, complete with cake and balloons, during one of the refreshment breaks. In addition, attendees can view the 2008 meeting program and see what has changed in the ATMP space and which topics are still going strong.



To register for this meeting, visit www.pda.org/EU/atmps2018

Data Integrity in Manufacturing Systems Technical Report Team | PDA Headquarters

(l-r) Derek Smith, Mylan; Anil Sawant, PhD, MSD; Els Poff, Merck; Carmelo Rosa, U.S. FDA; Jim Curry, Teva; Rebecca Parillo, FDA; John Grealis, Novartis; Jeffrey Broadfoot, Emergent BioSolutions; Christopher Smalley, PhD, ValSource; Denyse Baker, PDA; Anthony Warchut, PAREXEL

Joint PDA/Pharmaceutical Manufacturing Forum (PMF) Task Force Meeting
January 15–19 | Venice

Members of the joint PDA/PMF task force on achieving zero defects for visible particulates meet face-to-face at Ca' Foscari University.

11 Ways to Improve Your Leadership Skills

Margaret Buj

Whether you are aware of it or not, on some level you are continually leading yourself and others. Consider these 11 tips for how to improve your leadership skills and think about ways you can implement them in your daily life at work.

1. Have a clear vision

Take the time to share your vision, your mission and your goals with your team. Your job as a leader is to provide a clear path that your team can follow. Your team also must understand why the goals you have set are valuable to them. Take the time to explain to them, in detail, why and how your vision will not only improve the business, but how it will benefit them in return.

2. Know and utilize your strengths and gifts

You have unique gifts, leadership skills you were born with and personal strengths you have developed over your lifetime. Realizing these gifts and strengths and applying them will assist you in being a formidable leader.

3. Be Passionate

Passion is one of the most important leadership skills! Great leaders have a *genuine passion and enthusiasm* for their projects. Start by thinking of different ways you can express your zeal. Let people know that you care about their progress. When one person shares something with the rest of the group, be sure to tell them how much you appreciate their contributions.

4. Live in accordance with your morals and values

Making choices aligned with your morals and values helps you succeed almost as effortlessly as key leadership skills. People sense integrity and will naturally respect your leadership.

5. Serve as a role model

The best leaders walk the walk and talk the talk. As a result, group members admire these leaders and work to emulate these behaviors. If you want to become a better leader, work on modeling the qualities that you would like to see in your team members.

6. Set definitive goals and follow concrete action plans

You have to know your destination before you can map out a plan to get there. To improve your leadership skills, first set specific life goals with appropriate timelines. Design your goals by moving backwards from the end of your life to the present week. Then, formulate action plans you can commit to that will get you where you want to be.

7. Maintain a positive attitude.

No one respects a grumpy or negative person. With a positive attitude, you are looking at the bright side of life. People are naturally attracted to others who have a positive attitude. By being positive, you will lead a happier life and surround yourself with other positive people.

8. Improve communication skills

Having great leadership skills includes being able to clearly and specifically communicate your vision, goals, skills, intentions and expectations to others. It also includes listening to what other people have to say and how they are communicating.

9. Motivate others to greatness

The greatest leaders are those who embrace everyone in their sphere of influence by recognizing each person's unique value. To be one of these leaders, look beyond the obvious and see others with insight and compassion.

10. Admit failures and weaknesses and learn from them

Face it—no one is perfect. Everyone has made a mistake or two in their lives! The most successful leaders know that the key to success is not in avoiding falling or failing, but to learn from their mistakes. As a strong leader, you will also be able to communicate your weaknesses to your team, so that you and your team can determine who excels at that particular task or activity to balance the load.

11. Continue to educate and improve yourself

Great leaders not only demonstrate effective leadership skills but, most importantly, they continue to improve themselves in every possible way. The person who thinks he is an expert has a lot more to learn. Never stop learning. Be receptive to others' perception and to information you glean from the world around you. Always grow and learn.

About the Author

Margaret Buj is an Interview and Career Acceleration Coach who specializes in helping professionals get any job they want at their best-ever salary.

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Contact **David Hall,** Vice President, Sales, *PDA*, at hall@pda.org or +1 (240) 688-4405.

pda.myindustrytracker.com/en/buyersguide

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SNAPShot

PDA Task Force Meets Face-to-Face in Venice

Jahanvi (Janie) Miller, PDA

In January, Stevanato Group's **Paolo Golfetto,** cochair of the joint PDA/Pharmaceutical Manufacturing Forum (PMF) task force on achieving zero defects for visible particles, welcomed the task force to a face-to-face meeting at Ca' Foscari University in Venice.

During the two-day meeting, the task force worked together to align on a common, harmonized rationale to support a practical industry-wide guidance, intended for use with existing compendial, regulatory and industry standards. This would then be used to better identify visible particulate matter. Multiple workgroups within the task force met to identify a visible particle-size threshold, review the gap analysis done for analytical methods (elastomer and glass components) and develop validation strategies. The full task force, comprised of pharmaceutical manufacturers and suppliers, agreed that providing a well-balanced perspective on best practices best served all parties involved.

The task force has identified gaps in current risk assessments and methods used to detect and quantify visible particles. As a result, it has developed FMEAs for elastomer and glass components to help identify where the highest risk areas are for particulate contamination throughout the manufacturing process, and how to effectively control these risks. The task force will be seeking to validate their methods in the coming months to ensure that best practices are being applied, and that appropriate corrective actions to mitigate risks are being taken.

PDA cordially thanks the Stevanato Group for hosting the full duration of this meeting, especially recognizing Golfetto, **Mauro Stocchi** and **Gianmaurizio Fantozzi** for organizing the tour of the OMPI, Optrel and SPAMI glass manufacturing facilities as a kickoff for Phase 2 of this ongoing initiative. PDA would also like to thank all the staff who made themselves available to support the 20+ task force members over those two days: **Alessandro Zannini, Riccardo Stocco, Gaetano Baccinelli** and **Omar Pastrello** from APAMI and **Alessandro Morandotti, Alessandro Faidutti** and **Barbara Lucato** from OMPI. **[Editor's Note:** Photos from this meeting can be found on p. 15**.]**

Journal *Top 10*

Particulate Matter, E&L Topics of Interest to Journal Readers

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

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

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

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

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

5. Review
Edward C. Tidswell and Tim Sandle, "Microbiological Test Data—Assuring Data Integrity" January/February 2018

6. Review
Fran L. Degrazio, "Holistic Considerations in Optimizing a Sterile Product Package to Ensure Container Closure Integrity" January/February 2018

7. Case Studies
Ana M. C. Santos, et al. "A QRM Discussion of Microbial Contamination of Non-sterile Drug Products, Using FDA and EMA Warning Letters Recorded between 2008 and 2016" January/February 2018

8. Research
Galen H. Shi, et al. "Impact of Drug Formulation Variables on Silicone Oil Structure and Functionality of Prefilled Syringe System" January/February 2018

9. Research
Dennis Jenke, et al. "Simulated Leaching (Migration) Study for a Model Container-Closure System Applicable to Parenteral and Ophthalmic Drug Products" March/April 2017

10. Research
Jeffrey R. Vieregg, "Inhibiting Sterilization-Induced Oxidation of Large Molecule Therapeutics Packaged in Plastic Parenteral Vials" January/February 2018

Sterilizing Grade Filters and PUPSIT

A Statement From Four Filter Manufacturers

Recent statements made by European regulators to justify the pre-use/post-sterilization integrity test (PUPSIT) require clarification.

The statements indicated that filter manufacturers have weaknesses within their quality control functions that may create risks, thereby, requiring a pre-use, post-sterilization integrity test (PUPSIT). The statements included:

- Filter manufacturers have no transport qualification and lack control over the transport of the filter elements shipped
- Filter manufacturers do not control the outsourced gamma sterilization of their filter units, and, therefore, do not detect weaknesses
- The quality control of the filter manufacturing processes and the release criteria are insufficient and weak
- An anecdotal conversation alluded to an experience of a filter flaw that was masked by blockage of the filter

We believe these statements require substantial clarification.

Clarification

The four filter manufacturers involved in this joint position would like to address the statements made by the European regulators by describing the facts of filter manufacturers' quality systems.

- Packaging, transportation and handling are qualified by the filter manufacturers according to industry standards. Packaging designs are appropriately tested to assure the filter is properly protected. Packaged filters are shipped via different methods for a length of time to verify that the filters and packaging withstand typical means of transportation. Similarly, handling of the filters is well described to the end user through written instructions and training reiterated to the end user.

- Filter manufacturers rigidly manage the quality systems of critical raw material suppliers, control the incoming specifications of critical raw materials, control the filter manufacturing process and, finally, test finished product to assure performance within quality specifications. The release criteria of finished filters are well defined, documented and stringently controlled. In addition, all filter manufacturers have documented robust change control systems implemented to assure that the quality of the materials used, and of the finished filter goods, consistently stay at the highest level.

- Any external activities, for example, gamma irradiation of filters or single-use assemblies, are well qualified together with the external source. The outside sources are audited by the filter manufacturers, as defined by their quality systems, on a frequent basis to determine that the specifications are properly fulfilled and that consistent quality is assured.

- Similarly, the quality systems and the manufacturing processes of the signatory filter manufacturers and their third-party gamma irradiators are routinely audited by end users. These audits are proof that the manufacturing processes are well defined, documented and appropriately controlled to consistently deliver a high quality product.

- The results of the anecdotal conversation, that filter flaws are masked during processing and will not be detected by a post-use integrity test cannot be verified by the filter manufacturers.

We trust that this position paper provides clarification for the justifications that some regulatory authorities may use to require the performance of PUPSIT. Filter manufacturers are very well aware about their responsibilities in regard to delivering high quality sterilizing grade filters consistently.

MilliporeSigma
Sartorius Stedim Biotech
Meissner
Pall

[Editor's Note: The above is a response from four filter manufacturers concerning PUPSIT requirements in the European Union. This does not represent an official PDA position.**]**

*Published online first
letter.pda.org

Glass Along the Value Chain

Certain Treatments and Their Impact on Extractables for Borosilicate and Aluminosilicate Glass

Claudia Heinl, PhD, Schott

Protecting medications from harmful environmental influences and preserving their efficacy during shelf life are two of the most pressing challenges for both packaging manufacturers and pharmaceutical companies.

In particular, packaging materials must adhere to stringent regulations. U.S. regulations state that: "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" ***(1).*** This is also reflected in EU regulations ***(2).***

For this reason, high-quality borosilicate glass containers are currently the preferred primary packaging material, even for the most sensitive drugs. But as new glass compositions enter the market, how do these measure up? The case study below seeks to answer this question.

According to the current U.S. and European pharmacopeias, borosilicate glass contains significant amounts of boric acid, aluminum oxide, alkali metal oxides and alkaline earth metal oxides. Furthermore, due to the chemical composition of the borosilicate glass, it bears high hydrolytic resistance and, therefore, is classified as a Type I glass container ***(3).*** The resistance against water attack is assessed according to two test methods: the glass grains test and the inner surface test. Both of these determine the sodium extraction (including calcium and potassium expressed as sodium oxide equivalents) of glass after a certain stress procedure (autoclaving).

The result of the glass grains test directly depends on the composition of the glass, and—provided the composition is not changed—remains constant. On the other hand, the hydrolytic resistance of the inner surface tends to be negatively affected during the transformation of a glass tube into a container (converting).

A Salty Comparison Study

Whereas the root cause for resistance, and all other influencing factors along the value chain, are well known and have been intensely studied for borosilicate glasses, information is lacking for other glass types, such as aluminosilicate glasses. Consequently, a comparative study of aluminosilicate and borosilicate glass was performed for each step of the value chain with regard to the influence of converting and post-treatments on the extractables level for each glass type. This study specifically focuses on the conversion and ion-exchange process.

Here, the amount of network modifiers (sodium, calcium, magnesium, potassium) extracted from the inner surface of the glass tubing is compared to the respective amount extracted from the vial (i.e., after converting of the tubing). Since a glass might require an ion-exchange process after converting, a surface test is also performed on the vials following this chemical treatment **(Figure 1).**

The tubing sections, as well as the vials (nominal volume: 2R), are filled with ultrapure water and autoclaved for one hour at 121 °C per ISO 4802-2 ***(4).*** The analysis of the extracted elements is performed by means of ICP-MS and ICP-OES. Since the surface area exposed to

the water is different for tube sections (the end is closed by a stopper, so a smaller glass surface comes in contact with water) and vials (due to a glass bottom, more glass surface comes in contact with water), the results are given in µg/cm². This is a surface-correlated value, allowing for an exact correlation between tubing sections and vials. **Figure 2** shows the results obtained, given as oxides. Right from the

Figure 1 Value Chain

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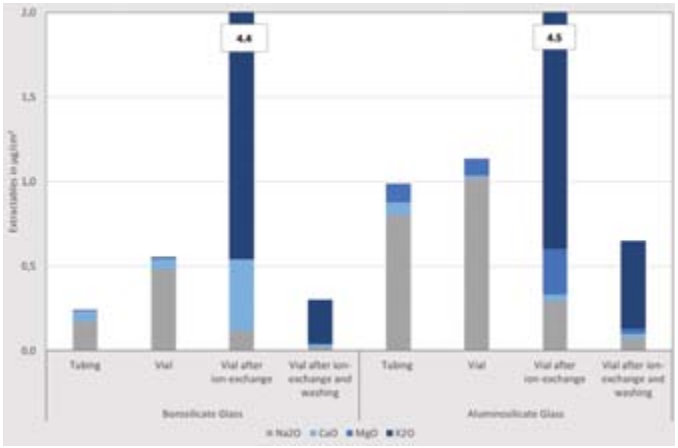

Figure 2 Extractables from Borosilicate and Aluminosilicate Glass after Autoclaving with Ultrapure Water (1 h, 121°C)

start, namely for the glass tubing, the amount of extractables is shown to be more than 400% higher for aluminosilicate glass compared to borosilicate glass (sum of network modifiers: 0.99 µg/cm² vs. 0.24 µg/cm²), as has also been reported in a previous case study published in the *PDA Letter* ***(5).***

Figure 2 also shows that, for both glass types, the levels of extractables increase after conversion of the glass tube into a vial. For borosilicate glass, this is mainly due to evaporation of volatile components such as alkali borates. This phenomenon, including all possible influencing factors, has been heavily studied over the last few decades and, thus, is well understood and clearly under control.

Also for the aluminosilicate glass type a negative, albeit, smaller influence of the converting step is demonstrated. Since there is no boron present in the aluminosilicate glass type, however, an alkali borate evaporation cannot explain the increase of sodium extraction after forming of the aluminosilicate glass vial. In consequence, the root cause of this increase remains unclear and needs to be investigated.

Going one step further, the greatest increase can be seen for a glass vial after the ion-exchange process. During this post-treatment, also referred to as chemical strengthening, the container is dipped into a liquid salt bath, exchanging sodium ions from the near-surface region of the glass with potassium ions from the salt bath. Since both glass types contain significant amounts of sodium this treatment can likewise be applied for aluminosilicate glass as well as borosilicate glass. The effect on the extractables level is as follows. As expected, the amount of sodium decreases, yet potassium dominates the level of extractables. Here, it amounts to 3.9 µg/cm² for borosilicate (total 4.4 µg/cm²) as well as for aluminosilicate glass (total 4.5 µg/cm²). Thus, the potassium extraction of a glass vial after the ion-exchange process (3.9 µg/cm²) is found to be more than six times higher than the combined extraction level of all network modifiers (sodium, calcium, potassium, magnesium) of an untreated borosilicate glass vial (sum: 0.6 µg/cm²). This might be due to residues of the potassium salt (e.g., potas-

The study indicates that glass vials cannot be used for packaging directly after a strengthening/ion-exchange process

sium nitrate) on the inner surface of the glass, although the procedure laid down in ISO 4802-2 (subchapter 8.2) already includes a cleaning procedure of rinsing with water at least five times ***(4).***

With an appropriate washing step, it is possible to remove residues of a potassium salt layer so that the amount of extractables is significantly reduced. As expected, the extraction profile of the network modifiers is still dominated by potassium oxide. Keep in mind, the level is even lower compared to the untreated vial: 0.30 µg/cm^2 versus 0.55 µg/cm^2 for the borosilicate glass and 0.65 µg/cm^2 versus 1.14 µg/cm^2 for the aluminosilicate glass. This is an absolute prerequisite for the aluminosilicate glass, since the post-treatment not only needs to eliminate the negative effect of the ion-exchange process but is also indispensable for reducing the high level of extractables of the untreated aluminosilicate glass.

With respect to the regulatory requirements, generally speaking, a higher amount of extractables means a lower chemical and hydrolytic resistance. To determine the compliance with the Type I requirements, the results of this case study are expressed as sodium oxide equivalents (Na_2O, CaO, K_2O) following the regulatory prescriptions of ISO 4802-2 and the European Pharmacopoeia, respectively (see **Figure 3**) ***(3, 4).***

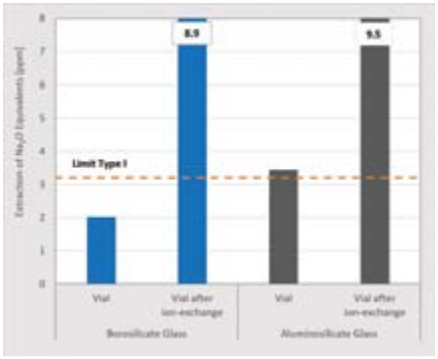

Figure 3 Hydrolytic Resistance According to ISO 4802-2 with the Individual Oxides (Na_2O, K_2O, CaO) Expressed as Sodium Oxide Equivalent

Continued on page 35

Know Your Numbers for Analytical Similarity

Emanuela Lacana, PhD, U.S. FDA

Despite an increase in the approval of biosimilars in the United States, the development of biosimilar products continues to be challenging. Some questions about them have been partially resolved, such as the number of lots needed for the analytical similarity exercise, while others are still under discussion.

Many questions remain regarding statistical analysis. To assist manufacturers, the U.S. FDA issued a draft guidance on statistical approaches to evaluating analytical similarity that clarifies several aspects of the statistical analysis; however, challenges remain when it comes to the use of statistical tools. For example, what does it mean for analytical similarity when an attribute does not meet statistical analysis criteria?

A well-known challenge for biosimilar developers resides in the ability to understand and capture the variability of a reference product. A biosimilar developer has no knowledge about the historical manufacturing range for the reference product and product release/stability specifications. This challenge is only partially mitigated by developers acquiring sufficient lots of reference product over time. As a result, developers may have an apparent narrow product quality window of the reference product, which may lead to relatively narrow acceptance criteria for analytical similarity testing. Furthermore, it may be challenging to develop a robust manufacturing process that delivers a product with consistent quality characteristics which, in turn, makes the development of an adequate control strategy equally challenging.

At the *2018 PDA Biosimilars Workshop,* industry and regulators will discuss the latest challenges and regulatory updates around analytical similarity. Questions to be addressed include: what specific challenges have industry and regulators encountered for analytical similarity, and what other gaps have been identified during development of biosimilar products? Ultimately, this workshop will examine the challenges and promise of available statistical tools for analyzing similarity.

2018 PDA Biosimilars Worshop

Washington, D.C.
Sept. 26–27
www.pda.org/2018biosimilars

2018 PDA Universe of Pre-Filled Syringes and Injection Devices

Moving the Patient to the Forefront

David Haase, Genentech, and Manfred Maeder, PhD, Novartis

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It can mean *better user-interfaces making devices simpler to use*. With more focus on human factors, devices are being designed from the start to be easier to use. As many of our newer drugs serve patients who are older or more physically or mentally impaired, this has become even more important. Training devices to assist patients with proper device use are much more common now.

It can mean *fewer injections*. Over the past few years, we have developed more concentrated formulations and delivered larger volumes of many drugs that have allowed patients to dose less frequently. Better technologies have enabled us to deliver those larger volumes and more viscous solutions.

It can mean *"smarter" devices*. Reminders to take the drug on time can improve patient adherence and help with drug effectiveness. Patients can be prompted through steps in real time to use the device properly. A device can also communicate to the patient, the healthcare provider and insurer to help ensure the patient is following their drug regimen.

It can mean *safer devices*. Sharps protection is becoming more common. New materials are helping reduce syringe breakage potential. Anticounterfeiting approaches and universal device identification systems are protecting patients from adulterated drugs.

Learn more about what it means to be patient-centric at the *2018 PDA Universe of Pre-Filled Syringes and Injection Devices.* See great posters, hear important presentations on these and other key topics in our industry, network with colleagues old and new and visit more than 100 industry exhibitors.

2018 PDA Universe of Pre-Filled Syringes and Injection Devices

Orlando, Fla.
Oct. 8–9
www.pda.org/2018pfs

2018 PDA Upcoming Events

SAVE THE DATE for PDA's 2018 Events

APRIL

17-18
2018 PDA Biopharmaceuticals: From Drug Substance Manufacturing to Final Product
Seoul, Korea
pda.org/2018Biopharma

17-18
Quality Culture Transformation Resources
Mainz, Germany
pda.org/EU/AprTransform2018

19-20
PDA Biopharmaceuticals Conference Course Series
Seoul, Korea
pda.org/2018BiopharmaCS

19-20
SOLD OUT
PDA Quality Culture Transformation – *Regulators Only*
London, UK
pda.org/2018AprTransform

23-27
SOLD OUT
Freeze Drying in Practice
Osterode am Harz, Germany
pda.org/EU/fdp2018

23-27
■ **PDA Visual Inspection Course Series – Option 1**
Bethesda, MD
pda.org/2018AprVI

24
2018 PDA Packaging Science Interest Group Workshop
Bethesda, MD
pda.org/2018Packaging IG

24-25
Vaccines Conference
Malaga, Spain
pda.org/EUVaccines2018

25
2018 PDA Visual Inspection Interest Group Workshop
Bethesda, MD
pda.org/2018VisualIG

MAY

1-4
Regulatory and Compliance Course Series
Bethesda, MD
pda.org/2018RCCS

7-11
■ **PDA Aseptic Processing – Option 3 Week 2: Jun. 4-8**
Bethesda, MD
pda.org/2018aseptic3

8-9
Virus Forum
Florence, Italy
pda.org/EU/Virus2018

14-15
2018 PDA Sterile Medicinal Products Manufacturing Conference
Bethesda, MD
pda.org/2018Sterile

15-17
■ **Validation of Moist Heat Sterilization Processes – Option 1**
Bethesda, MD
pda.org/2018MayVMH

17
Annex 1 Workshop
Dublin, Ireland
pda.org/EU/Annex2018

21-24
■ **Fundamentals of Aseptic Processing – Option 2**
Bethesda, MD
pda.org/2018MayFundAP

21-25
PDA Lyophilization Course Series
Bethesda, MD
pda.org/2018Lyo

29-30
Pharmacopoeia Conference
Vienna, Austria
pda.org/EU/pharma2018

JUNE

5-6
Advanced Therapy Medicinal Products Conference
Amsterdam, The Netherlands
pda.org/EU/ATMPS2018

7
Practical Application of Phase-Appropriate GMP & Quality to Clinical Development of ATMPs
Amsterdam, The Netherlands
pda.org/EU/TCATMPS2018

7-8
PDA Quality Culture Transformation
Bethesda, MD
pda.org/2018JunTransform

12-14
Quality Risk Management Facilitator Training
Bethesda, MD
pda.org/2018Facilitator

13-14
2018 PDA Container Closure Performance and Integrity Conference
Bethesda, MD
pda.org/2018CCPI

18-21
■ **Fundamentals of Aseptic Processing – Option 3**
Bethesda, MD
pda.org/2018JunFundAP

25
Interest Group Meeting: Freeze Drying
Berlin, Germany
pda.org/EU/IGFreezeDrying2018

25
Interest Group Meeting: Quality Systems
Berlin, Germany
pda.org/EU/IGQualitySystems2018

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

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

25-27
PDA Quality Course Series
Bethesda, MD
pda.org/2018QCS

26-27
3rd PDA Europe Annual Meeting
Berlin, Germany
pda.org/EU/Annual2018

26-27
■ **Isolator Technology**
Bethesda, MD
pda.org/2018JunIT

28-29
Practical Approach to Quality Culture
Berlin, Germany
pda.org/EU/quality-culture2018

28-29
Best Compliance Practices at the GMP Testing Laboratory
Berlin, Germany
pda.org/EU/Compliance2018

28-29
Test Methods for Pre-Filled Syringe Systems
Berlin, Germany
pda.org/EU/TestPFS

JULY

9-12
Quality Risk Management Certificate Program
Bethesda, MD
pda.org/2018QRM

23-23
PDA Aseptic Processing – Option 4
Week 2: Aug. 13-17
Bethesda, MD
pda.org/2018Aseptic4

30-1
■ **PDA Environmental Monitoring Course Series**
Bethesda, MD
pda.org/2018JulEMCS

31-1
2018 Mold Identification for Quality Control
Bethesda, MD
pda.org/2018Mold

AUGUST

2
NEW COURSE
Addressing Biofilm and Other Non-Routine Microbial Events
Bethesda, MD
pda.org/2018Biofilm

20-23
PDA Biotechnology Course Series
Bethesda, MD
pda.org/2018Biotech

20-24
PDA Cleaning Course Series
Bethesda, MD
pda.org/2018CCS

ADDITIONAL SIGNATURE EVENTS IN 2018

SEPTEMBER

26-27 **2018 PDA Biosimilars Workshop**
Washington, DC | *pda.org/2018Biosimilars*

OCTOBER

8-9 **2018 PDA Universe of Pre-Filled Syringes and Injection Devices**
Orlando, FL | *pda.org/2018PFS*

10 **2018 PDA Combination Products Workshop**
Orlando, FL | *pda.org/2018Combo*

15-16 **PDA Europe Pharmaceutical Microbiology**
Berlin, Germany | *pda.org/EU/PharmaMicro*
(Some sessions simulcast with PDA North America)

15-17 **13th Annual PDA Global Conference on Pharmaceutical Microbiology**
Bethesda, MD | *pda.org/2018Micro*
(Some sessions simulcast with PDA Europe)

17-18 **2018 PDA Endotoxins Workshop**
Bethesda, MD | *pda.org/2018Endotoxins*

NOVEMBER

6-7 **Outsourcing & Supply Chain: A 360° View**
Seville, Spain | *pda.org/EU/Outsourcing2018*

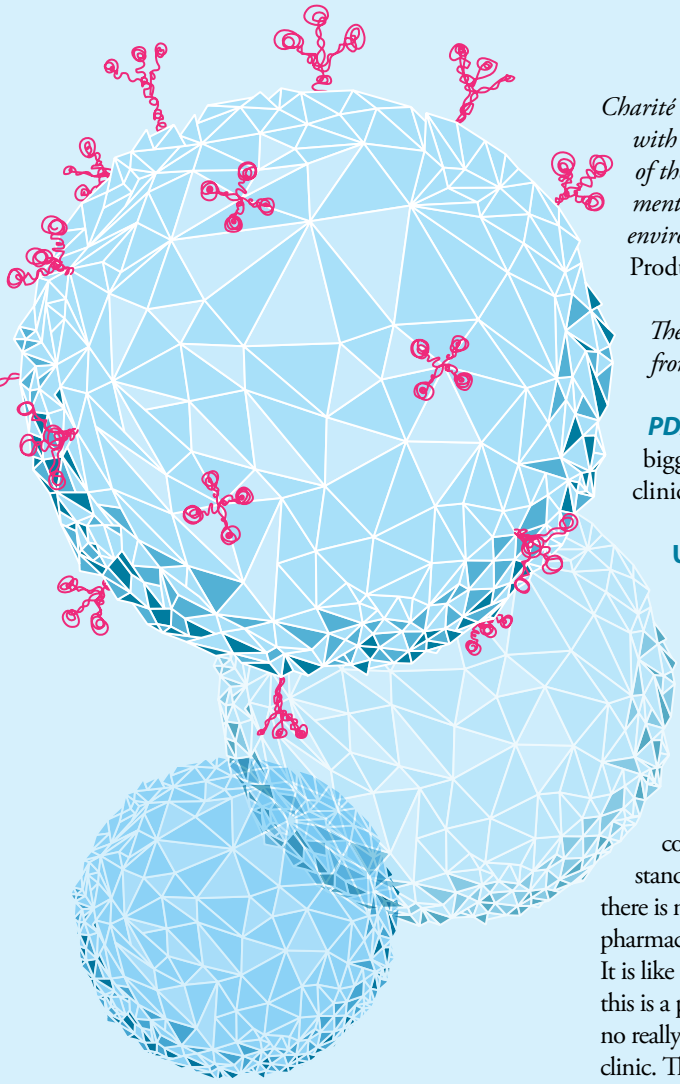
27-28 **11th Workshop on Monoclonal Antibodies**
Seville, Spain | *pda.org/EU/MABS2018*

27-28 **Pharmaceutical Freeze Drying Conference**
Seville, Spain | pda.org/EU/FreezeDrying2018

Speaking the Language of GMP

An interview with Dr. Lutz Uharek

Rebecca Stauffer, PDA



Charité – Universitätsmedizin Berlin is the largest university hospital in Europe, affiliated with both Humboldt University and Freie Universität Berlin. ***Lutz Uharek,*** *MD, Head of the Stem Cell Facility at Charité – Universitätsmedizin Berlin, is leading development of a new stem cell facility, moving cell production from a clinical setting to a GMP environment. He is also the Chair of this year's PDA Europe* Advanced Therapy Medicinal Products *conference in Amsterdam, June 5–6.*

The Managing Editor of the PDA Letter *interviewed Uharek about his experience moving from a clinical operation to a GMP environment.*

PDA Letter: What has been your biggest challenge with moving from a clinical operation to a GMP facility?

Uharek: The biggest challenge is that our clinicians are going from more flexible processes and routines; classical GMP is based on more robust and inflexible processes. I think there is also a different language. Although the topic is the same, the language is more about risk management and quality control. In the hospital, you have standards for quality assurance; however, there is no common language between the pharmaceutical world and the clinical world. It is like speaking German or French. I think this is a problem. Of course, we often have no really robust processes and routines in the clinic. The physicians and other personnel have to deal with frequently changing situations. This is a different world compared to classical pharmaceutical production where things are usually running on a more standardized and routine basis.

PDA Letter: How are you addressing that "language barrier," so to speak?

Uharek: We currently have "quality circles" consisting of people working in both worlds. People coming from the GMP field, from quality control, from quality management and product manufacturing and people coming from the clinical world who would like to use these products, or are using these products mainly within clinical trials, so they are most interested in connecting production and clinical evaluation. We are currently bringing these people together to speak a common language.

PDA Letter: How has your institution applied key engineering principles in its migration to GMP?

Uharek: I am personally very interested in lean management, especially considering I wrote my master's thesis about it. I believe that thinking in processes and thinking modular is key to ending up with robust and reproducible processes and routines, even if you are dealing with a very flexible role. You have to split things up into basic processes that can be controlled and, then, you can pull these together to move processes to the next level. To think in this more process oriented and modular way is essential, in my opinion, to ending up with reproducible and controllable processes in upscaling, beginning with the first small batch to production to large-scale manufacturing.

Too Much Light a Problem?

PDA Letter: What has it been like working with regulators?

Uharek: They have been very supportive mostly. One advantage, of course, is that they often understand the clinical need behind the problem, and it is relatively easy from the hospital point of view to

> **Everyone is looking in the place they are most familiar with. Everyone is looking where the light is**

convince them there is a problem that has to be solved in order to bring beneficial therapies to the patient. In other words, the general attitude is helpful.

The problem I see is that the regulatory agencies, companies and clinics are working together in the new field of ATMP development, and the danger is that we all are looking for problems in areas we are familiar with. I like to call this problem the "streetlight effect." There is a joke I heard about a drunkard searching for something under a streetlight. A police officer happens upon him and asks "what are you doing?"

"I am looking for my keys, I lost them in the park," replies the drunkard.

"Then why are you looking under the streetlight?"

"Because this is where the light is."

The problem is known from social sciences. Everyone is looking in the place they are most familiar with. Everyone is looking where the light is. Regulators are looking intensively at problems of sterility, management of the cleanrooms, and so on. And on the other hand, clinicians are looking mainly at things happening on the hospital ward. But they are not looking at the production stage where something critical might have happened.

All sides should be aware of the "streetlight effect," and should help each other to bring light in the areas where the problems are really located. The "key" technology helping regulators, ATMP-manufacturers and clinical personal to identify dark areas containing a problem will be risk management.

PDA Letter: How can academic institutions, regulatory agencies and manufacturers collaborate to address the challenges of this new field?

Uharek: The most important point really is to work together. Coming together and discussing all these critical issues is the most important thing. The other essential point for me is working on a general understanding of risk management. We need risk management, risk evaluation, that involves all stakeholders, this is very important to focus on with all parties that are involved, kind of risk management circles.

Another important point is to work more modular, to think in terms of processes to allow approval of routine processes and technologies instead of finalized product.

First, there should be more focus on risk and, second, on processes that can be put together for production lines.

PDA Letter: Based on your experience, what do you see as the future design of GMP-processing spaces for ATMPs?

Uharek: Again, I think the future design of GMP processing will be modular. It will be flexible. It will be process oriented. I am convinced we will not have these classical cleanroom, GMP facilities in ten years, at least not for the field of ATMPs. Medicine will become more personalized and we will have more and more smaller batches. We will have a very trial period of product development, which will also include manufacturing technologies and, therefore, we will have to work with flexible, modular, closed-system production technologies.

We have to avoid more rigid buildings that were perhaps appropriate for classical pharmaceutical production which usually was unchanged for ten years or longer. Instead we will often have production times of only one year and very small batches, and for that reason, we will need other types of technologies.

PDA Letter: Naturally, all these changes mean partnering with suppliers. In the past, ATMP manufacturers have been limited due to the small pool of available suppliers. Do you see this changing?

Article at a Glance

- Switching from clinical operations to GMP requires learning new language
- Avoiding the "streetlight effect"
- Still some space for sterility test

Interested in learning more? Other sessions will explore the nature of GMPs for ATMPs at this year's *Advanced Therapy Medicinal Products,* June 5–6 in Amsterdam. Learn more at www.pda.org/eu/atmps2018

Uharek: Yes, definitely. We are in contact now with companies coming from different fields that are realizing that this more-personalized type of production—you can call it "microfactories" or modular, closed-production systems, and so on—is something being asked for by a couple of companies producing ATMPs in the field of genetic engineering. And the field of cell therapies is evolving dramatically, so there is clearly a need for these cellular production technologies, say for CAR-T cells and genetically modified stem cells. And a couple of suppliers already have realized the solutions that have to be developed for this different type of production.

We are working together—and I think this is something very fruitful—we are working very closely together with technology providers in the development of new manufacturing technologies for ATMPs. One problem is that you have to validate your processes with biological, often human, cells, so you need to be close to the hospital, to the manufacturing site and to human material in order to validate your manufacturing equipment and processes, and also quality controls. For that reason, I think it is very important that cooperation exists between suppliers and these organizations, such as GMP units, that are located near the hospital, to improve and to speed up the development of new technologies.

New Purpose for Sterility Tests

PDA Letter: What does the short shelf life of these products mean for sterility testing?

Uharek: We are very familiar with products with short shelf lives in the routine use of stem cell products for the treatment of mostly hematological disorders. Hundreds of thousands of these products have been shipped all over the world to treat patients with stem cell transplants. Then, we have this problem of sterility assurance. We cannot wait with a transplant or treatment unless we have all the information together.

What we do is a kind of conditional release for these products with what we have in terms of sterility testing. Perhaps there is a need to develop more effective tests for a quick testing procedure, but in the end, I think it will always be the case that you have situations where you have to release the product without complete sterility testing. In that case, I think it is still very important to have this data available, not to protect patient from a critical infection—which is not possible in this case— but perhaps to provide a prophylaxis if it is known that the microbiological testing was positive.

The most important reason to perform extensive sterility testing and contamination control is to improve your processes. First, to realize where you have critical problems and, second, coming back to the streetlight effect, to bring light into the dark, such as what it means to have a particular contamination. It is often the case that we put this product, harboring bacteria, into immunodeficient patients. Perhaps they have an infected central line. These positive microbiological results are something we have to learn and gather data on. What it means if such a product is contaminated, and what is associated with the contamination? And how does the particular microbe impact the clinical outcome?

This is a very important point to me. It is necessary to combine GMP and GCP and to learn the effects. Could this be infectious? This could also be a problem of liability or problems associated with characterization of the product: how do these quality parameters affect the outcome on the clinical side? This is essential for ATMP development, that we have a very close [working relationship] between the manufacturing and the clinical sides to initiate such a learning process.

What we need is a learning system that allows the regulators to look at the system, and to allow risk-based adjustments.

Quality assurance could be less strict. You need a better control in situations where you have not so much knowledge about your processes, and you do not need [control] any longer if you have very well established processes. This is something that has to be built up—both from outside, from the regulators, and from inside from the people evaluating these ATMPs in the clinic and those manufacturing the product.

PDA Letter: In that case, based on your experience, does it make sense for academic institutions to build their own research facilities? Or would it be better to collaborate with the industry?

Uharek: I see a need for different solutions. It really depends on the products. On the one hand, we have products that are used in a very dynamic clinical situation where any failure in logistics has dramatic implications and where you have to be very flexible. For such products, near hospital production might be preferable. Or we have situations where we have orphan indications, rare diseases, where you have to establish something like a Center of Excellence. In such situations it might be more appropriate to have centralized hub-based production.

We will also have products where time is not a critical factor and where production problems, logistics issues and manufacturing failures are not so critical for the patient. In such situations or when you can repeat the process because the product is not so expensive, it is definitely better to be more on the side of classical pharmaceutical production with a centralized and very well controlled production unit or manufacturing facility. I think there might also be a place for something in between.

We have to look first at the need for the patient, the characteristics of the product and then to see how this can be brought in the best way to the patient. Then we have to ask the question, 'how can that be done in a lean way with the lowest efforts and with minimum resources?' I think this is how the decision should be made about where and how production of ATMPs should take place.

About the Expert

Lutz Uharek, MD, is a hemato-oncologist and senior physician at Charité – Universitätsmedizin Berlin's Center of Oncology.

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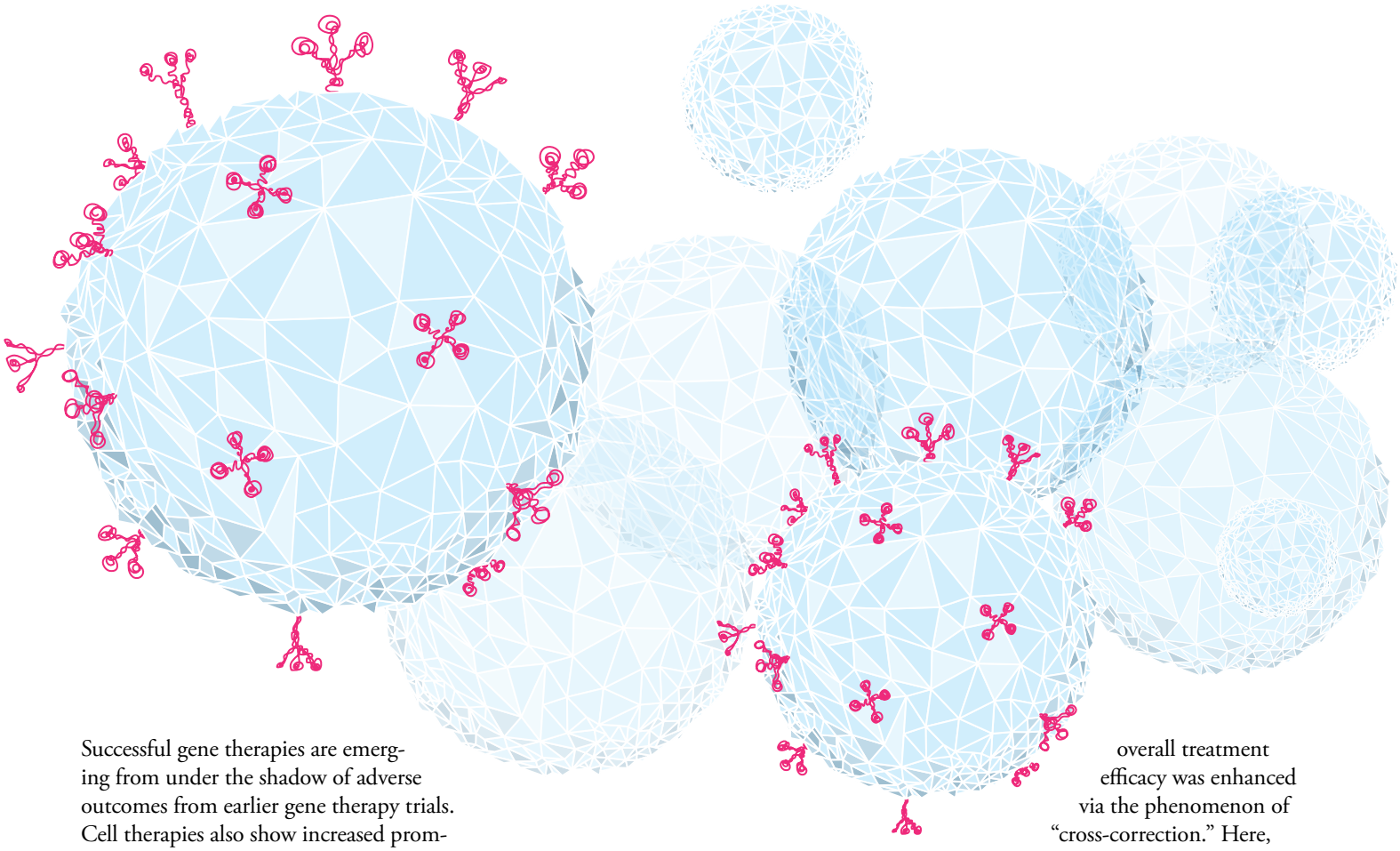
Cell and Gene Therapies Present Challenges, Promise

Joshua Eaton, PDA



Successful gene therapies are emerging from under the shadow of adverse outcomes from earlier gene therapy trials. Cell therapies also show increased promise. A growth in technological understanding and more advanced process control and verification strategies have improved the safety and efficacy of new treatments using cell and gene therapies.

But how will these new therapies be realized? Are these innovative products ready to move from the clinic to commercial production? And what do regulators think?

The *2017 PDA Cell and Gene Therapy Conference* held in San Diego, Dec. 5–6, presented a comprehensive blend of perspectives from academia, industry and regulators regarding process development and validation for a variety of promising gene and cell therapy treatments for cancers and other difficult-to-treat ailments.

James Wilson, PhD, University of Pennsylvania Perelman School of Medicine, discussed a potential treatment for spinal muscular dystrophy (SMD), a disease in which an infant/toddler reaches no developmental milestones (e.g., talking, moving the head, rolling over) and rarely survives beyond 18 months of age. One of the causes of SMD was found to be a deficiency in gene expression for a specific protein. Wilson's team was able to introduce a gene therapy treatment with adeno-associated virus 9 vectors to preserve protein and gene expression that resulted in some remarkable, beneficial outcomes for 11 of 12 patients involved in the clinical trial:

- Eleven of the 12 could talk and move their heads
- Nine gained the ability to roll over
- Two achieved the major developmental milestone of walking independently

Not only was the administered vector successful in transducing the targeted cells, overall treatment efficacy was enhanced via the phenomenon of "cross-correction." Here, cells actively transduced by a viral vector transfer the corrected gene to non-transduced cells. This then induces those cells to properly express the gene and resultant protein.

In addition to this advancement, the Children's Hospital of Philadelphia Raymond G. Perelman Center for Cellular and Molecular Therapeutics has teamed up with Spark Therapeutics to develop treatments for retinal defect repair and hemophilia B. Spark Therapeutics Chief Scientific Officer **Federico Mingozzi**, PhD, described their joint efforts to derisk gene therapy development and the successful synergy that can occur between academia and industry. This resulted in both therapies providing long-term efficacy (>1 year) in initial trials.

Planning for Manufacturing Success

For a look at another innovative product,

Michael Paglia, Senior Director, CMC Operations, Oncorus, presented an overview of Oncorus' miRNA-based therapy to produce an oncolytic virus to treat glioblastoma multiforme. Successful planning, technology transfer and analytical methods allowed administration of the treatment via direct, intratumoral injection rather than diffuse systemic delivery. For any pharmaceutical company, let alone one specializing in gene and cell therapies, the need to consider the end product and how to move from concept to manufacturing (i.e., how will it be delivered? What product composition is required? What production scale will be required?) is an ever-present concern. Paglia and Mingozzi agreed that process lifecycle knowledge and understanding are crucial for success in this challenging therapeutic arena.

This focus on product knowledge, process control and lifecycle management is being successfully implemented at BlueRock Therapeutics. The company has developed technology to reliably and safely create an allogeneic cardiac cell therapy with induced pluripotent stem cells (iPSCs) instead of embryonic stem cells (ESCs), avoiding the ethical and regulatory issues associated with ESCs. As described by **Robert Deans,** Chief Technology Officer, BlueRock, their approach can generate cardiomyocytes of different types (e.g., left versus right ventricle, pacemaker cells, etc.) which can then fully integrate electrically with existing heart cells. Additionally, BlueRock has been able to demonstrate that there are no residual iPSCs and, therefore, no risk of tumor-forming cells circulating in the patient. This is accomplished via genomic integrity and safety testing for tumorigenicity and teratogenicity using whole genome sequencing, instead of other, more limited techniques (e.g., G-band karyotype, SNPs, or whole exome sequencing).

Regardless of individual company successes, gene and cell therapy process control and verification, including comparability studies, can be inherently difficult since, for many products (especially autologous treatments), a batch may be specific to just one patient. **Ernest Bognar,** Vice President, Operations, Gradalis, Inc., presented some strategies and considerations for designing an autologous cellular immunotherapy manufacturing plant for clinical, and eventual, manufacturing scale. In this scenario, decisions must focus on logistics and product/material expiry, centralized versus decentralized production, technical capbility for portability to other facilities or contract manufacturing organizations (CMOs), aseptic processing needs and total capacity compared to capacity utilization. Analyzing these factors requires an extensive cross-functional team as well as establishing communication with CMC reviewers from regulatory agencies.

With regard to small batch sizes, Novartis is addressing this within their cell therapy products. **Yoko Momonoi,** Senior Fellow, Novartis, presented the company's efforts ➤

to conduct comparability studies for an autologous cell therapy. She noted that, while the U.S. FDA has issued a draft guidance on comparability protocols ***(1),*** there are currently no specific guidances on this topic. Companies can use ICH Q5E: *Comparability of Biotechnological/ Biological Products Subject to Changes in their Manufacturing Process* ***(2),*** however, as a baseline along with careful review of an internally developed flowchart of comparability assessments. Additionally, Novartis' use of healthy donor cells as surrogate material has been useful for evaluating process changes.

Data Can Show a Full Picture

Thomas Chittenden, PhD, VP, Statistical Sciences, and Founding Director of Advanced Artificial Intelligence Research Laboratory at WuXi NextCODE, also explored use of internal data. He showed how using massive datasets and intensive statistical analysis could provide predictive modeling and deep learning in biosciences. With these tools, the industry could begin to evaluate whole genomes for the potential benefit of certain treatments (e.g., patient has a protein that makes a drug better accepted by their body).

All the promise of successful outcomes, however, still hinges upon safe delivery of the treatments to the patient. **Kimberly Carnes**, Associate Director, Quality Systems, REGENXBIO, discussed the company's implementation of quality systems using an externalized model for manufacturing and testing. In order to succeed with a highly outsourced manufacturing model, REGENXBIO needed to balance internal requirements (QA staff and procedures) with external requirements (suppliers). This required an iterative approach to implementing the quality system, and, at the outset, simply picking a starting point and then building upon that base. Some portions were settled at the beginning, such as data integrity procedures and identification of critical suppliers. Policies for supplier oversight (CMOs, CTLs, etc.) were implemented, and then strengthened as the company gained knowledge and experience through tracking and trending supplier deviations and lab investigations at the sponsor site.

> **"Regulatory requirements still include validated lot release assays and understanding of process variability, potency assays, etc.,"**

One key element was to ensure that REGENXBIO personnel supplemented these investigations and CAPAs as needed.

Zenobia Taraporewala, PhD, CMC (Product) Reviewer, FDA provided the regulatory perspective regarding these innovative therapies. She noted that many new therapies focus on pediatric applications where there is a crucial need to balance minimal risk with the prospect of a positive outcome. Considering these criteria, the FDA may deny phase 3 studies if manufacturing controls are deemed inadequate (reinforcing Bognar's assertion to engage with CMC regulators early and often). Overall, Taraporewala admonished companies to approach cell and gene therapy product development with purpose and consideration. Regulatory requirements still include validated lot release assays and understanding of process variability, potency assays, etc., which cannot be achieved without the efforts previously mentioned. Along with lot release criteria, product stability is also required, including within the final container. Additionally, an understanding of critical quality attributes and critical process parameters is crucial and comparability must be shown for any process changes. Although the products and processes may be new and generally unknown, it is still expected that statistical robustness be commensurate with the phase of the product (development, engineering, clinical, etc.).

Given all of these hurdles, Taraporewala noted that regulators are open to dialogue about common issues associated with cell and gene therapy production. It is understood these novel products will initially have assays that are not sufficiently developed and validated. While concurrent validation with a single lot is possible, the lack of data hinders this route. Also, by nature of the patient population, there may well be fewer clinical lots and insufficient retention samples for comparability studies and generation of data to support proper statistical analysis. As the products progress from clinical to manufacturing scale, stability studies may not have enough nor the right kind, of data collected (e.g., omitted shipment data). The novel nature of the product and processes also raises concerns regarding compatibility with delivery devices and if there are cobranding/copackaging considerations

In the end, all the speakers agreed that the challenges are many for successful development of a gene or cell therapy—from knowledge regarding the method of action and potency and small lot sizes to limited stability data related to formulation, storage and shipping. It all points to the promise of the field and the need for intensive data collection and process knowledge to successfully develop treatments for patients in need. Another *PDA Cell and Gene Therapy Conference* is scheduled for October. PDA is proud to offer ongoing support to these efforts through conferences, technical reports and the newly formed Cell and Gene Therapy Interest Group.

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Glass along the Value Chain continued from page 23

Figure 3 highlights that a 2R borosilicate glass vial without any treatment is, as expected, well below the Type I limit. Yet, the untreated vial made of aluminosilicate glass exceeds the Type I limit and, therefore, would only meet Type III requirements. After the ion-exchange process, the amount of Na_2O equivalents is roughly three times the limit value of a Type I glass for both glass types (8.9 ppm for borosilicate glass, 9.5 ppm for aluminosilicate glass). The negative influence of this treatment on the extractables level is apparent. The study indicates that glass vials cannot be used for packaging directly after a strengthening/ion-exchange process, and, as a consequence, further treatment or leaching process must be applied in order to fulfill regulatory requirements.

In summary, the amount of extractables depends on the glass type, yet also changes significantly throughout the value chain increasing the risk of inaccurate comparisons. Starting from the initial level of the tubing, the negative influence of the converting and ion-exchange process on the extractables profile of both glass types, borosilicate as well as aluminosilicate glass, is shown. Compared to borosilicate glass vials, aluminosilicate glass vials after converting, i.e., before the ion-exchange process, show a high amount of extracted elements that makes untreated aluminosilicate glass containers unfit as parenteral primary packaging material. As a consequence, further treatments or leaching processes should be applied on aluminosilicate glass containers before they may come into contact with the drug.

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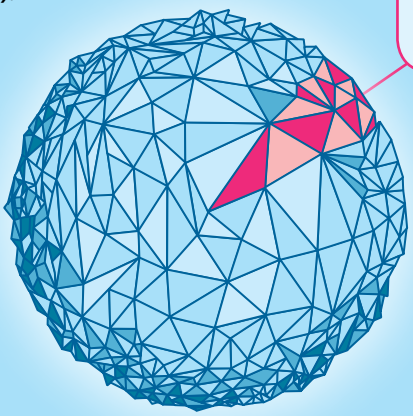
About the Author

Claudia Heinl is a Product Manager for SCHOTT Pharmaceutical Tubing.

Cell and Gene Therapies By the Numbers

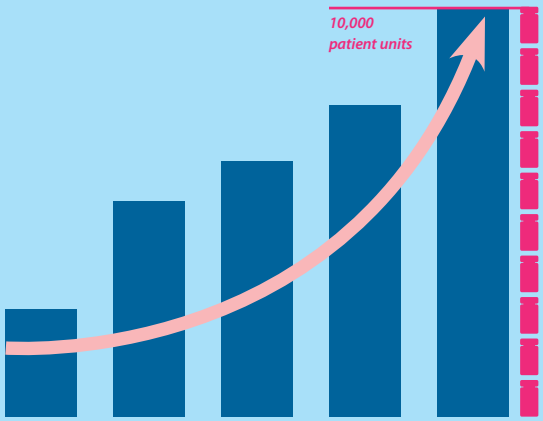
The number of clinical trials for *gene therapies reached its peak* in 2015 at **163 trials** that year ***(1).*** And 12–14 investigational gene therapies are expected to reach regulatory approval in the next 2–3 years ***(2).***

In 2017, **6.2%** of biomanufacturers in a survey identified cell therapies as the *single most important trend* ***(3).***



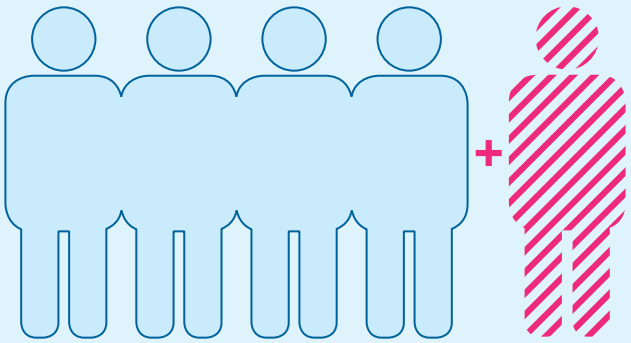
Clearly the field of cell and gene therapies shows promise. But is the capacity there to support manufacturing?

Current cell and gene therapy production is *about 10,000 patient units per year* ***(4).***
Concerns about cleanroom/facility design, staffing levels and expertise also impact capacity ***(4).***



But the picture is not so bleak…

The number of cell and gene therapy manufacturing facilities has risen in the United Kingdom, with a **20%** *increase in the number of people employed in this space* ***(5).*** And contract manufacturing and development organizations (CDMOs) will play a key role in producing these critically needed products ***(6).***



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2018 PDA Container Closure Performance and Integrity Conference

Assuring Packaging Quality in Delivery Systems

At the *2018 PDA Container Closure Performance and Integrity Conference*, learn about the new challenges and latest developments for assessing container closure integrity and system performance, including:

- Protecting the drug product across the product lifecycle
- Considering container design features to enhance functionality and usability
- Applying standard and novel container closure integrity testing technologies
- Investigating drug product intrinsic interactions with delivery and device systems
- Developing strategies for ensuring delivery and device systems performance and integrity
- Understanding novel drug product container filling/sealing processes

Explore topics related to containment, delivery and device systems integrity, and performance evaluations.

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Upcoming PDA Conference to Draw From Annex 1 Commenting

Hal Baseman, ValSource

PDA recently completed a thorough review of the revision of *EU GMP Annex 1, Manufacture of Sterile Medicinal Products,* which was released for public comment on Dec. 20, 2017. The Annex 1 revision represents an important restatement of the EU regulatory position on sterile product manufacturing, both for aseptic processing and terminal sterilization. As the PDA commenting team prepared their comments, it became apparent that challenging questions remain for regulators and our industry. These questions are not limited to those posed by the Annex 1 revision; they are symptomatic of an industry struggling to meet the challenges of modernization and globalization. In short, challenges every technology-driven industry faces.

These questions include the following. What is the industry's understanding around true risk- and science-based decision-making when it comes to aseptic processing? How can a balance be achieved between increased monitoring and reliance on robust sterility assurance design, such as when additional tests may increase risk to product quality? What are the limits of traditional testing methods? And what does the industry need in order to facilitate adoption of new technologies to manufacture and control product?

If these questions make you feel uncomfortable, they should. Because much of the way we think about them may be changing. And as they say, facing and addressing change should be a bit uncomfortable.

To help the industry and our members answer these questions, PDA is hosting a timely *Sterile Medicinal Products Manufacturing Conference* in Bethesda, Md., May 14–15. The conference planning committee, comprised of experts from industry and regulatory agencies, designed this event to bring together the sterile products community to discuss contemporary approaches for sterile product manufacturing through case studies and personal experiences. A special focus of the conference will be a review of the proposed Annex 1 revision and recommendations from the commenting team. The conference will also cover the following sterile product manufacturing and control essentials, among others:

- Updates on relevant PDA technical reports, USP chapters and global regulatory trends
- Sterilization and terminal sterilization challenges
- Environmental, personnel and product contamination control strategies
- Isolators and barrier systems
- Filter and container integrity testing
- Quality systems and quality risk management

Change is becoming ever more necessary, influenced by the expansion of global manufacturing, the availability of knowledge, the discovery of promising therapies and the availability of new technologies.

We as an industry must ask these difficult questions and explore new ways to address them to ensure the improvements that will be required in the 21st century. We recognize that it is time for the industry to face the challenges with the objective of implementing certain and effective process improvement.

If you are responsible for decision-making, design, validation, control, operation, maintenance or management of sterile medicinal product manufacturing, or if you influence those who are, understanding the discussions, regulatory expectations, challenges and ways to meet these challenges today is essential. For more information, visit www.pda.org/2018sterile.

In addition to this conference, PDA Europe will also host three one-day meetings in Spain, Ireland and Germany to cover the impact of Annex 1. The first meeting will be held May 17 in Dublin. To register, visit www.pda.org/EU/Annex1_Dublin.

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Awareness Key for Container Closure Components: Part II

A Summary of the 2017 PDA Container Closure, Devices and Delivery Systems Workshop

[Editor's Note: Part I of "Awareness Key for Container Closure Components" was published in the March issue. Session moderators for the *2017 PDA Container Closure, Devices and Delivery Systems Workshop* summarized their respective sessions. The article can be read in its entirety, complete with figures, on the Letter website**.]**

Plenary 2: Strategies for Safety Evaluation

Moderator: Ronald G. Iacocca, PhD, Research Fellow, Device and Delivery Research & Development, Eli Lilly and Company

A critical aspect in device development is assurance of safety. With this in mind, **Kathleen Lin,** PhD, Associate Senior Consultant Engineer, Eli Lilly, presented approaches to biocompatibility evaluation of combination products. Safety information can be found in literature, clinical experience or predicate usage, but animal studies may be required. Depending on the device application, there are multiple in vivo and in vitro tests with various endpoints that need to be considered. Important factors for determining test requirements include the nature and duration of bodily contact as well as the chemical and functional properties. Not everything needs to be tested if existing data can be leveraged. She suggests using a technical justification to minimize animal testing, if necessary. In general, Lin recommends testing "smart" versus testing everything. Additionally, suppliers should be engaged early on in the process.

Khaudeja Bano, Abbott Diagnostics echoed other speakers who noted the need for organizations to adopt an integrated product development process that blends essential requirements for quality-by-design (QbD) for drugs as well as for design controls for devices. She described the clinical and safety parameters to consider for device/drug/biologic combination products from a combination products viewpoint. By July 2018, the new rule for postmarketing safety reporting for combination products goes into effect. Combination-product applicants must comply with the reporting requirements applicable to the type of marketing application used to approve or clear their combination product. Additionally, combination product applicants must also comply ➤

2018 PDA Sterile Medicinal Products Manufacturing Conference

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- Sterilization and terminal sterilization challenges
- Process monitoring, testing, and design
- Environmental, personnel, and product contamination control strategies
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with a subset of six specified reports based on the other constituent parts (drug, device or biological product).

Plenary 3: Leachables and Extractables for Combination Products that Include Both Drugs and Devices

Moderator: Kim Li, PhD, DABT, MPH, Senior Manager, Amgen
Chemical characterization and biocompatibility testing are critical for the qualification of device/drug combination products. In recent years, both industry and regulators have shown increasing interest in using chemical characterization (i.e., extractables/leachables) to inform and reduce certain biocompatibility testing requirements.

This session began with a presentation by **Christopher T. Houston**, Director of Analytical Chemistry, iuvo BioSciences, on PQRI's strategy for assessing extractables and leachables compounds in orally inhaled nasal drug products and parenteral and ophthalmic drug products. **Piet Christiaens,** Scientific Director, Toxkon Europe NV, and **Matthew Woods,** Senior Chemist, Lancaster Laboratories, presented jointly on conducting extraction studies. They emphasized that USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems and PQRI guidances were not prescriptive; rather, they offer flexibility for designing extractables and leachables studies. The collaborative presentation provided points to consider for justifying extraction conditions (e.g., solvent selection, extraction time, temperature), as well as for processing of test materials (e.g., sterilization).

Jennifer Goode, Biocompatibility Program Advisor, FDA, CDRH, discussed the highlights of the 2016 FDA guidance on the use of ISO 10993-1: Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process. The new guidance focuses on how to use risk management to address biocompatibility and to leverage existing testing, with scientific justification. The key to a favorable biocompatibility review involves chemical characterization in conjunction with toxicology information from the literature. This is consistent with the goal of refining/reducing/replacing animal testing. Goode provided a case study involving absorbable drug-eluting stents, which illustrated how to conduct a biocompatibility assessment using chemical characterization and toxicology risk assessments. This case study used the stent (absorbable device) as the primary mode of action and the drug as the secondary mode of action.

Plenary 4: Holistic Safety and Quality Assessment

Moderator: Ronald G. Iacocca, PhD, Research Fellow, Device and Delivery Research & Development, Eli Lilly and Company
The safety assessment (i.e., toxicological evaluation) of extractables and leachables is a cornerstone of pharmaceutical development programs. But the approaches to assessing extractables and leachables impurities vary widely among device, drug and device/drug combination products. While the toxicological assessments follow the principles and methods of the ICH guidance on impurities and the ISO standards on leachable substances, the impact of these impurities to the quality attributes is largely unknown.

Packaging Critical to Success of Drug Products

Diane Paskiet, West, and Lei Li, Eli Lilly

The ultimate goal of any pharmaceutical company is for patients to have access to safe and effective medicines. An integral container closure and delivery/device system plays a critical role in ensuring product quality and patient safety at every stage of the drug product lifecycle. How can we design a container closure system to enable drug delivery that provides comfort and convenience for patients, and ultimately, improves treatment outcomes?

A drug product has numerous quality requirements throughout its lifecycle, from development to commercialization, post-approval change and continuous improvement. At every stage throughout the process, the drug must be protected from the detrimental effects of the various components used in the processing, manufacturing, storage and delivery of the final product. How can we ensure the new packaging design features provide adequate containment and protection for sterile products and demonstrate suitability for the intended use under the various environments to which they are subjected?

These will be among the issues presented in Bethesda, Md., June 13–14 at the *2018 PDA Container Closure Performance and Integrity Conference*. This event will focus on the most current topics related to containment, delivery and device system integrity and performance. Here, you will learn about the latest developments for assessing container closure integrity and system performance, including:

- Protection of the drug product across the lifecycle
- Integration of the drug with delivery system development
- Container design features to enhance functionality and usability
- Application of standard and novel container closure integrity testing technologies
- Considerations for container closure systems used in cryogenic applications
- Drug product intrinsic interactions with delivery/device systems
- Strategies for ensuring delivery and device systems performance and integrity
- Risk-based systems approaches to designing studies
- Novel drug product container filling/sealing processes

The continued advancement of innovative therapies is transforming the way container and drug delivery systems are designed, developed and manufactured. Container closure systems can no longer be developed in isolation. The cross-disciplinary understanding of drugs, biologics and delivery devices and a systems approach to integrating packaging development into a drug delivery system have become a required skillset for all working in this field.

2018 PDA Container Closure Performance and Integrity Conference

Bethesda, Md.
June 13–14
www.pda.org/2018ccpi

Kim Li, Senior Manager EHSS Toxicology, Amgen, described the challenges with the toxicology assessments of extractables and leachables impurities originating from biomanufacturing, primary drug containers, drug delivery devices and drug-delivery device combination products. The common theme to the different approaches was the need for robust chemical characterization to enable toxicology risk assessments. Through extractables profiling, potential leachables of concern could be assessed for clinical relevance and exposure scenarios. Further, extractables profiles can be screened for compounds with reactive functional groups that may pose a risk of covalent binding with protein therapeutics, leading to structural modifications and impact to quality attributes.

Dan Mellon, Pharmacology Toxicology Supervisor, FDA, CDER, provided candid and in-depth insights on the review of extractables and leachables information in product registrations and submissions. Some noteworthy pitfalls include:

- Lack of, or inadequate, extractables and leachables information to justify safety of container closure/drug delivery system
- Inappropriate qualification thresholds for data interpretation of extractables and leachables
- Insufficient sensitivity of the analytical method to detect compounds of concern
- Poor description on how extractables data were used to design leachables studies

Mellon provided resources and practical advice for registrants to avoid these common pitfalls. He used case studies to detail the rigor of the FDA review process required for pharmacology/toxicology/CMC reviewers. Mellon also included points to consider for new leachables assessments in line with the best practices for lifecycle management for marketed products. His conclusion emphasized the importance of communicating early and providing substantial amounts of data.

[This is the second of three installments, the third will appear in the May issue.]

PDA Europe Conference on Advanced Therapy Medicinal Products

ATMPs: What a Difference a Year Can Make

John Geigert, PhD, BioPharmaceutical Quality Solutions

What we observed this past year might be the early signs of a tsunami for a new class of biopharmaceutical products: living viruses and cells. These signs include recent regulatory approvals of a genetically engineered virus to treat patients with vision loss, genetically engineered T-cells to treat patients with acute lymphoblastic leukemia and large B-cell lymphoma and a genetically engineered virus to treat patients with melanoma. Additionally, in the United States, the 21st Century Cures Act accelerates FDA review of regenerative medicine advanced therapies. In Europe, EMA has revealed that, out of the 30 medicines that have received their PRIme MEdicines (PRIME) designation, one-third are advanced therapy biologics.

Regulatory authorities recognize the importance of moving these products through clinical development, but they also recognize that the transfer of these advanced therapy manufacturing processes from universities or hospitals into appropriate GMP and quality system compliance for human clinical studies is a major challenge.

Patients using these products need to be protected, and these new living biopharmaceutical products have unique challenges **(Table 1).**

	Protein-based Biopharmaceuticals	Virus- and Cell-based Biopharmaceuticals
Product Class	Non-living recombinant proteins and monoclonal antibodies	Living genetically engineered viruses and cells
Manufactured Batch Size	One batch serves 100's or 1000's of patients	One batch size serves 1 patient
Product Purification	Extensive chromatography and filtration processes available to control for process- and product-related impurities	Viruses can be chromatographed, but cells limited to washing; very high safety concern about materials used in the manufacturing
Batch Traceability	All released product batches are considered comparable	Wrong batch to wrong patient could kill them
QC Samples	Usually more than adequate amount of samples available for testing	Limited batch size puts major constraints on sample availability
QA Batch Release	Completed prior to inventory release	Frequently all required testing is not completed prior to patient administration
Manufacturing and Quality Unit Link to Clinician	Independent of clinician	Critically linked to clinician collecting the patient cells, and then timing for clinician administration of product batch

Table 1 Unique Challenges for Protein-based and Virus/Cell-based Biopharmaceuticals

For the protein-based biopharmaceuticals, GMP and quality systems are well developed and, when implemented correctly, have served and protected patients during clinical development very well. But because of the unique challenges presented by the living virus- and cell-based biopharmaceuticals, these systems have to be adapted in a practical, common-sense way.

At the end of the PDA Europe conference, *Advanced Therapy Medicinal Products,* in June, the following course will be offered, "Practical Application of Phase-Appropriate GMP & Quality to Clinical Development of ATMPs." This course will discuss common sense and regulatory-compliant CMC approaches to appropriately and adequately protect patients both during the transfer from a university/hospital into a patient, and during the clinical development of these advanced therapy medicines. For more information and to register, visit www.pda.org/EU/TCATMPS2018.

About the Author

John Geigert is President of BioPharmaceutical Quality Solutions, which specializes in providing CMC regulatory strategy consulting for the biopharmaceutical and biologics industry. He has more than 35 years of CMC industrial experience.

PDA Supports Science in Industry

Michael Sadowski, Baxter

Our mission at PDA is to advance pharmaceutical manufacturing science and regulation so that our members can better serve patients. This is encapsulated in our accompanying motto: "Connecting People, Science and Regulation®."

Science serves as the foundation for all we do at PDA. Accordingly, PDA's Science Advisory Board (SAB) has been commissioned to provide guidance and set strategic direction on technical topics associated with pharmaceutical manufacturing and quality science. SAB is also responsible for:

- Guiding the development of technical reports, Points to Consider documents and articles for the *PDA Journal of Pharmaceutical Science and Technology* and *PDA Letter*
- Supporting advancement of PDA's manufacturing science-focused interest groups and their activities
- Assisting with developing curricula and identifying instructors for PDA Education courses

To support these efforts, SAB consists of a diverse team of approximately 25 world-renowned, scientific thought leaders representing industry, regulatory agencies and academia. Currently led by **Maik Jornitz** (Chair) and **Phil DeSantis** (Vice-Chair), SAB receives strong support from PDA staff member **Jahanvi (Janie) Miller.**

I have been fortunate to be a member of SAB for nearly three years. And it has been a phenomenal personal and professional experience to participate in the technical (and sometimes very lively!) discussions within this esteemed core of scientific experts. SAB meets monthly, along with two face-to-face meetings each year. Throughout the year, we regularly discuss the development, review and balloting of technical reports, new initiatives and formal comments on global regulatory standards/guidance documents.

In addition to focusing on contemporary topics such as big data, cleaning validation, visible particulates and isolators, SAB recently began a concentrated effort to improve the state of sterile product manufacturing. While we also published Parts I and II of the *Points to Consider for Aseptic Processing* documents, some members of SAB organized a series of workshops to provoke active debate around identification of best demonstrated practices in this area. This effort recently culminated with the development and approval of formal PDA comments on the 2017 draft of the *EU GMP Annex 1, Manufacture of Sterile Medicinal Products.*

SAB provides strong and dedicated support to PDA's foundation of science which is critical to our mission and vision. If you are interested in learning more about SAB and its corresponding interest groups, please consult the following link: www.pda.org/scientific-and-regulatory-affairs/advisory-boards/science-advisory-board-(sab).

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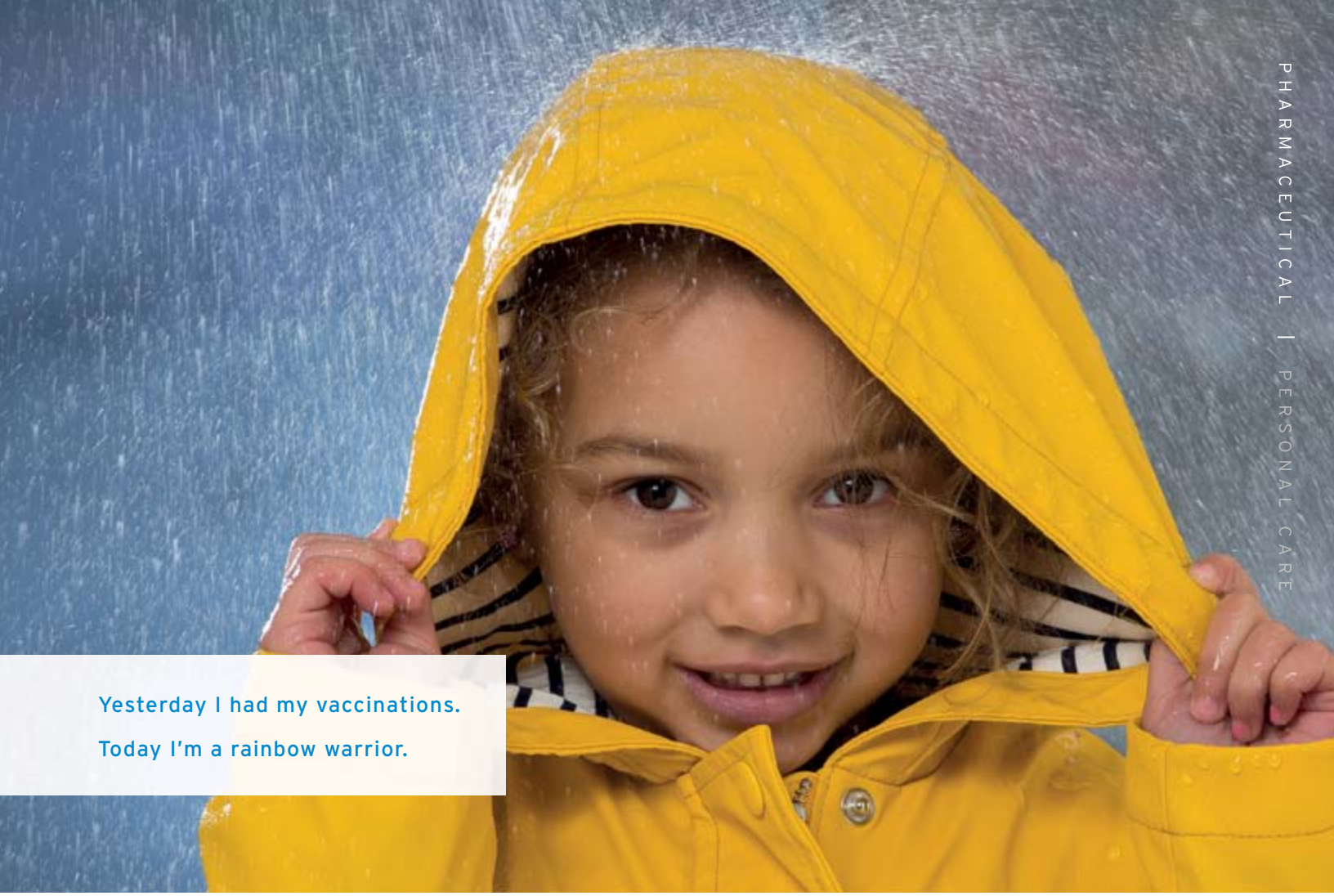

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