People • Science • Regulation

PDA Letter

Volume LIII • Issue 4 www.pda.org/pdaletter April 2017

Views on Advanced Therapy Medicinal Products

PDA®
Parenteral Drug Association

2nd PDA Europe Annual Meeting

Global Healthcare of the Present & the Future

12 June
Cleaning & Disinfection

12 June
Supply Chain Strategies for API and Drug Product

12 June
Quality by Design for Biopharmaceuticals

15-16 June
Introduction to Aseptic Processing Principles

15-16 June
Quality Culture

Register by 13 May 2017 and SAVE!

13-14 June 2017

Hilton Berlin

Berlin | Germany

pda.org/eu-AnnualMeeting2017

April 2017 PDA Letter

26

Viral Safety Approaches for Advanced Therapy Medicinal Products

Thomas R. Kreil, Global Pathogen Safety, Shire

The availability of plasma-derived medicinal products—one of the earliest achievements of medical biotechnology—has enabled great progress in the treatment of specialized conditions such as hemophilia and immune deficiencies. Yet early on, the biologic materials used to develop these products were also found to be vulnerable to infectious disease agents.

Cover Art Illustrated by Katja Yount

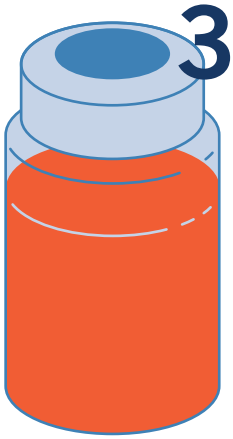
30

How to Get Your ATMP From the Lab to the Market

Andy Fry, Team Consulting

What is actually involved in taking an advanced therapy medicinal product (ATMP) from a brilliant idea in the lab to a successful product on the market? Is it similar to the development of a combination product? Or a monoclonal antibody? Just how difficult can it be? The level of activity surrounding ATMPs has been increasing, with some remarkable therapeutic opportunities currently being explored.

InfoGraphic



34

GMP Cycle for an Autologous Cell Therapy

This issue's infographic offers a general look at how an autologous cell therapy is manufactured under GMP conditions.

PDA Letter

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

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

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

Subscriptions are not available.

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

Departments

Digital Exclusives

> **On the Issue** | Defining the Quality Culture
Cylia Chen-Ooi, one of the members of PDA's quality culture subgroup of its quality metrics task force, talks about why quality culture is critical within the industry.

pda.org/letter

PDA GLOBAL HEADQUARTERS
4350 East West Hwy., Suite 600
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
info@pda.org
www.pda.org

PDA EUROPE — AM BORSIGTURM 60
13507 Berlin, Germany
Tel: 49 30 4365508-0
Fax: +49 30 4365508-66
petzholdt@pda.org

PDA TRAINING & RESEARCH INSTITUTE
4350 East West Hwy., Suite 600
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (240) 482-1659
info-tri@pda.org

PDA
Parenteral Drug Association

On the Issue Videos by the *PDA Letter*

Interviews with leading industry experts on the issues important to you

Watch the following experts:

AbbVie's Andrew Storey — Breakthrough Therapy Designation & Manufacturing

PDA Chair Martin VanTrieste — EU Serialization Rules

Merck's Michele D'Alessandro — Big Data & Pharmaceutical Manufacturing

PDA's Data Integrity Task Force

For more information on all PDA podcasts and other interviews, please visit:

www.pda.org/pdaletter

Letter to the Editor

In regard to the Letter to Editor from James Agalloco and James Akers published in the March 2017 issue of the *PDA Letter*

I do agree with the authors that there is no science-based reason for biological indicators (BIs) inoculated with 10^6 spores to be used for validation of vapor-phase hydrogen peroxide (VPHP) applications used for aseptic processing; however, the use of BIs with lower populations may not be as "globally accepted" as the authors imply.

The US FDA guidance document cited in the letter states that a 4- to 6-log spore reduction can be justified depending on the application. It goes on to state that, if decontamination methods are applied to certain product contact surfaces, a minimum of a 6-log reduction should be demonstrated. The 2007 version of the PIC/S guidance document, which is more recent than the document referenced in the letter to the editor, states that it is common practice to seek 6-log reductions of the BI organism for isolator applications.

The major supplier of VPHP BIs for aseptic processing applications offers products with 10^4, 10^5, and 10^6 spore inoculations. Over 90% of their VPHP BIs shipped have 10^6 inoculations, thus, confirming the comment in the PIC/S guide. It will take substantial data that has been published in refereed journal articles to convince many people to depart from what they perceive as the industry "norm."

— Don Eddington

ATMPs Are Beaming Our Way

Advanced therapy medicinal products (ATMPs) will always hold a special place in my heart, because one of the very first articles I wrote for the *PDA Letter* was a summary of a session on cell and gene therapy manufacturing at the *2012 PDA/FDA Joint Regulatory Conference* ***(1).***

ATMPs appeal to the Trekkie inside me. Particularly, they bring to mind the scene in *Star Trek IV: The Voyage Home* where the crew travels to a circa. 1985 hospital. Here, **Dr. McCoy** gives an elderly patient a pill that enables her to grow a new kidney, much to the disbelief of the medical staff. I like to think that pill contained a cell or gene therapy! But I want to point your attention to two recent ATMP advancements that suggest the imagined world of *Star Trek* medicine is no longer so fictional.

The New England Journal of Medicine reported in March that French scientists working with the biotechnology firm BlueBird Bio used a gene therapy technique to remove the gene responsible for sickle cell disease in a French patient. According to the WHO, over 300,000 infants are born with some type of this extremely painful disorder each year. Gene therapies may be a way to stem this tide.

The second recent advancement is on the manufacturing side. Manufacturing of ATMPs is challenging, particularly as the GMP requirements have not caught up to this new type of product. And if a traditional batch manufacturer wants to move into the ATMP space, they may have to invest in equipment that supports small-scale manufacturing. This could require operator retraining and even redesigning the facility. All of this can lead to substantial costs, potentially impacting the pricing of these new therapies.

The solution to this may come in, of all places, a box. A March 8 article in *MIT Technolgy Review* highlighted gene therapy researcher **Jennifer Adair's** mobile lab, or "gene therapy in a box" solution. She modified an existing cell processing device so that it could almost entirely automate the process of preparing blood cells with an HIV gene therapy. The cells enter the box and then come out 30 hours later. In addition, Adair added wheels to the box, making it portable. While this mobile gene-therapy-lab-in-a-box is still far from a commercial reality, it offers a glimpse into the future of ATMPs.

I look forward to covering these developments on behalf of PDA as we move ever forward to that *Star Trek* future.

Rebecca Stauffer

Reference

1. Stauffer, R. "Challenges of Manufacturing Cell Therapy Products." *PDA Letter* 48 (October 2012): 19–22.

Correction

In the February issue, the term "SPS" in **Mads Reedtz Espersen's** article on page 22 was incorrectly translated as "Spark Plasma Sintering, a low voltage pulsed direct current sintering technique." It should have been translated as "Systematic Problem Solving."

PDA:
Taking the Lead on Post-Approval Changes

PDA's Post Approval Change: Innovation for Availability of Medicines (PAC iAM℠) program strives to identify, assess and address current barriers to implementation of post-approval changes to promote continued operations and to drive innovation and continual improvement.

Addressing these barriers will better ensure and sustain reliable global supply and availability of product to patients through the entire commercial lifecycle of a product.

Through the PAC iAM℠ initiative, PDA has available a number of valuable resources for the industry, including:

- Points to Consider Papers
- A Call to Action
- Informational Articles
- Webinar/Presentations
- 2017 PAC iAM Workshop, Sept. 13-14, 2017 Washington, DC

To access these important tools, visit www.pda.org/pac

PAC iAM Papers Available on PDA Journal Website

Two "PDA Papers" authored by members of PDA's Post-Approval Changes for Innovation in Availability of Medicines (PAC iAM) Task Force are now available in the "Accepted Articles" section of the *PDA Journal of Pharmaceutical Science and Technology* (http://journal.pda.org/content/early/recent).

The papers, "PDA Points to Consider: Technical Product Lifecycle Management: Communication and Knowledge Exchange between Marketing Authorization Holders and Health Authorities" and "PDA Points to Consider: Technical Product Lifecycle Management Pharmaceutical Quality System Effectiveness for Managing Post-Approval Changes," are open access manuscripts available to both PDA members and nonmembers. The two papers are part of an extensive workplan by the task force to address the need for improved post-approval change processes within the industry (for more information about the task force's activities, see p. 37).

The task force is currently conducting a survey and has begun work on a PDA technical report. In addition, there will be a workshop on post-approval changes Sept. 13–14, following the *2017 PDA/FDA Joint Regulatory Conference.*

Members of the PAC iAM Technical Report Team convened at PDA headquarters Jan. 5 to kickstart development of a technical report

"PDA Papers" are special contributions to the PDA Journal and represent the official viewpoint of PDA. The "Accepted Articles" section of the PDA Journal is for articles that have been accepted for publication but have yet to appear in an official edition, commonly referred to as "published-ahead-of-press," and are fully citable. PDA launched this capability in 2016.

Nominate BoD Candidates for the 2018–2020 Term

The PDA Nominating Committee is seeking recommendations from members for candidates to fill Board of Director positions for the 2018–2020 term. Nominees must be current PDA members in good standing. Recommendations will be considered and evaluated by the PDA Nominating Committee. This year's committee is chaired by Immediate Past Board of Director's Chair **Hal Baseman,** and includes current Board of Director's Chair **Martin VanTrieste** and Board of Director's Chair-Elect **Rebecca Devine**.

If you are interested in being considered or want to recommend a colleague, send the recommendation via email to nominate@pda.org or via mail to PDA Global Headquarters, Bethesda Towers, Suite 600, 4350 East West Highway, Bethesda, MD 20814, USA, attention: Nominating Committee. In addition to your recommendation, please include any other 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 or feedback about the nominating process, please feel free to contact PDA President **Richard Johnson** at johnson@pda.org or Hal Baseman at hbaseman@valsource.com.

PDA Volunteer Spotlight

David Hussong, PhD

- **Consultant**
- ***ValSource, LLC***
- Member Since | **1993**
- Current City | **Kensington, Maryland**
- Originally From | **Bethesda, Maryland**

The best solution may not always please everyone, but listen to as many perspectives as possible

Of your PDA volunteer experiences, which have you enjoyed the most?

My work on PDA task forces has been very rewarding, particularly with the team behind *Technical Report No. 33 (Revised 2013): Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods.* Here, I worked with some exceptional talent.

Recently, I have enjoyed participating in teaching at PDA's Training and Research Institute (TRI). This allows me to share my knowledge with the community.

You worked for the US FDA for many years. How did PDA help you as a regulator?

Interactions with PDA gave me an opportunity to learn from the industry. These were the people with the practical knowledge of a wide range of subspecialties in parenteral sciences. Integrating the practical with the regulatory expectations greatly enhanced my understanding of sterile manufacturing sciences.

Who would you consider your mentors?

As a PDA volunteer, I was honored to have worked with the late **Scott Sutton, Mike Korczynski,** and **Ed Fitzgerald,** all of whom were instrumental in many of the technical advances behind parenteral drugs. In addition, my volunteer work led me to become acquainted with other superb leaders in the industry.

You recently transitioned from FDA to a position with a consulting company. What advice would you give to members considering career transitions?

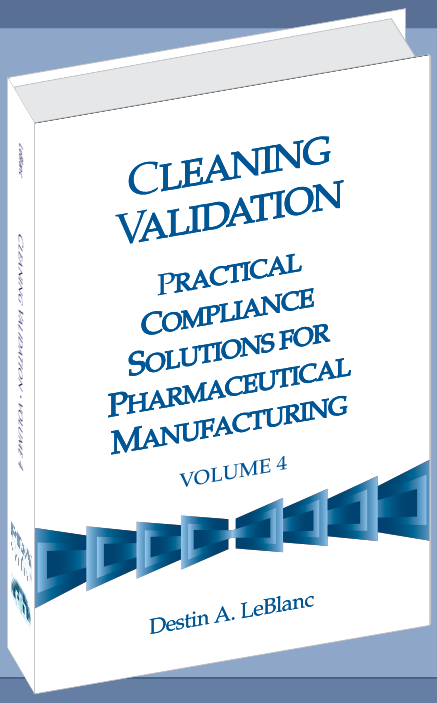
Transitions within the pharmaceutical industry can be very difficult, but finding the right fit will save a great deal of heartache. The focus should be more about the people you work with and how they support each other.

Were you always interested in microbiology?

Well, I nearly became an auto mechanic. As a college student, I worked on cars to support my tuition and living expenses. In my junior year, I entered the microbiology program and found my analytical skills were better suited to this field of science. But I still enjoy repairing things.

PDA Bookstore New Release

Pre-order and Save 15% through **April 30, 2017**
Enter campaign code **CV4** during Checkout.



Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing, Volume 4

BY: DESTIN A. LEBLANC

PDA MEMBER PRICE: ~~$240~~ $204

PDA NON-MEMBER PRICE: ~~$299~~ $254.15

HARDCOVER: ITEM NO. 17341

DIGITAL: ITEM NO. 18027

Volume 4 complements Destin LeBlanc's earlier three books on the same subject. This book modifies and updates LeBlanc's monthly *Cleaning Memos* originally published from January 2013 through December 2016. More than half of the chapters in the book are on setting limits in one way or another, so the use of health-based limits will require balanced reading (and thinking) for an overall understanding.

Each *Cleaning Memo* is presented as a chapter, with the chapters also organized by common topics. For example, topics related to setting limits are in one section, those related to sampling in another section and so forth. In all cases, the content focuses on changes for improving clarity and applicability as well as to modify the text with new information. There is one appendix with a list of acronyms used in this volume as well as a second appendix dealing with the author's shorthand method of expressing limits.

The author would also like to encourage pharmaceutical manufacturers, and particularly upper management, to meet the challenges of the science-based and risk-based approaches to cleaning validation. Using some of the principles and practices in this Volume may help in designing a more effective and efficient cleaning validation program.

go.pda.org/CV4

ABOUT THE AUTHOR

Destin A. LeBlanc is a consultant at Cleaning Validation Technologies. He has extensive experience in product development and technical services for cleaning and antimicrobial applications. He is an international lecturer on contamination control and has written widely on cleaning validation topics including four volumes in the *Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing* series published by PDA and DHI. He is a member of PDA and ISPE and trains FDA personnel on cleaning validation. He is a graduate of the University of Michigan and the University of Iowa.

Data Integrity Event Draws Largest Attendance Ever

Jeff Kisslinger, ProPharma Group, Missouri Valley Chapter Board Member at Large

PDA's Missouri Valley Chapter kicked off 2017 with a bang, hosting a free event on data integrity Feb. 6 in St. Louis. The event was a rousing success with more than 150 people attending—representing nearly all of the major pharmaceutical manufacturers in the area. The chapter chose the topic because of the increased number of data integrity violations cited by the US FDA in recent years. Chapter President **Keith Koehler** said it succinctly, "with the issuance of the new industry guidance document last year, we felt it was a great topic to serve our local industry."

As if having a free event wasn't enough, the chapter also collected donations for International Medical Relief (IMR), an organization that provides medical care to underserved communities or those that have been affected by natural disasters throughout the world. **Brianna Kempker,** Social Outreach Coordinator for the chapter and student at Lindenwood University, led off the evening by bringing IMR's message to attendees.

Andrea Briggs started off the session with her talk, "Data Integrity – Industry Approach to Compliance," which provided an overview of data generation and evolution, the impact of globalization, operational outsourcing, and documentation practices. She did a thorough job of explaining why data integrity plays such a critical role in the success of our industry.

(l-r) Bryan Lowery, Mallinckrodt Pharmaceuticals; Keith Koehler, Excite Pharma Services; James Polarine, Steris; Sharon Pederson (Thoma), FDA; Andrea Briggs, Mallinckrodt; Brianna Kempker, Steris

Next, Captain **Sharon Pederson (Thoma)** from the FDA presented the Agency's views on data integrity within the industry. She focused on specific issues such as FDA expectations for audit trail reviews, metadata, access to cGMP computer systems, and paper records. Her talk was well received, showing that is some truth to the saying "when the FDA speaks, people listen." It also didn't hurt that she is an excellent speaker!

There is some truth to the saying that "when the FDA speaks, people listen"

"With 150 attendees, this was the largest attendance for any PDA Missouri Valley event and the feedback from the audience was very positive," said Koehler, who added that the Missouri Valley Chapter is looking forward to continued success with its annual spring meeting this month.

PDA Who's Who

Andrea Briggs, Senior Manager of Quality, Mallinckrodt

Brianna Kempker, Intern, Steris

Keith Koehler, President, Excite Pharma Services

Sharon Pederson (Thoma), PharmD, National Expert of Pharmaceutical Inspections, FDA

PDA Photostream www.flickr.com/parenteral-drug

2017 PDA Pharmaceutical Quality Metrics and Quality Culture Conference

February 21–22 | Bethesda, Md.

(l-r) David Churchward, MHRA; Cylia Chen-Ooi, Amgen; Jeffrey Baker, PhD, US FDA

(l-r) Guy Villax, Hovione; Anders Vinther, PhD, Sanofi Pasteur; Robert McElwain, US FDA; Gerhard Koeller, PhD, Boehringer Ingelheim

(l-r) Thomas Friedli, University of St. Gallen; Cylia Chen-Ooi, Amgen; Marci Goldfinger, J&J; Jan Paul Zonnenberg, PricewaterhouseCoopers; Machelle Eppler, Patheon; Brianna Peterson, Boehringer Ingelheim

(l-r) Steven Mendivil, Amgen; Mary Anne Malarkey, CBER, US FDA; Ashley Boam, CDER, FDA; William MacFarland, CDRH, FDA; Tara Gooen Bizjak, CDER; Alex Viehmann, CDER

PDA Visitors | PDA Headquarters

The PMF Visible Particulate Task Force convened February 15 and 16 for a face-to-face meeting at the PDA headquarters in Bethesda, Md.

(l-r) Kirk Eppler, Genentech; Dawn Downing; Merck; Shelley Preslar (IG Leader), Azzur Group; Paul Kolosick, Merck

(l-r) Thomas Friedli, University of St. Gallen; Stephan Koehler, University of St. Gallen; Tara Gooen Bizjak, US FDA; Steven Mendivil, Amgen; Cylia Chen-Ooi, Amgen

5 Competency-Based Interview Questions

Margaret Buj

Competency-based interviews have become a standard practice by interviewers. A competency-based interview consists of a set of questions that test your knowledge of different areas specific to the job in question. They are also used to examine your outlook and attitude toward managing day-to-day tasks, problem-solving, and crisis handling. Competency-based questions often require candidates to present real-life examples of how they handled a specific situation.

Here are five typical competency-based questions you may be asked during an interview.

1 Your Level of Organization

Most, if not all, employers value highly organized candidates. Employees who are organized tend to be more productive. In addition, those in managerial roles perform better by providing project frameworks and details in a timely fashion and staying on top of tasks that need to be accomplished quickly.

Questions in this arena may examine how you managed several projects at once, particularly if you had to prioritize, or if you had to work on a project that involved multiple departments. Be prepared to answer questions on project management, managing communication, and securing assistance and tools to keep everything rolling smoothly.

2 Your Communication Skills

Communication skills are a must in any successful company, and you will be presented with questions on your communication skills at every interview you attend. Whether you are a good communicator via speech or writing, be prepared to discuss this essential skill with your employer, and indicate the type o f communication that bests suits you.

Questions in this arena usually include detailing situations in which your communication skills helped solve a problem or defuse a conflict; they may also inquire into a situation where your communication skills failed, and what you did to redress the problem. As with any question that asks about your failures, it is important to be honest—both about the failure and how you sought to address it.

3 Your Decision-Making Abilities

Good decision-making abilities are important. Many supervisors value employees who do not constantly need to be told what to do and are capable of making decisions about execution, prioritization, and methodology. Being a good decision-maker in difficult decisions is also a valuable quality, especially if you are applying for a supervisory position.

Expect to be asked about a time where you had to make a difficult or complicated professional decision, and whether it yielded positive or negative results. Be prepared to explain what you learned from either situation, and how these experiences may have improved your decision-making ability. Once again, be frank.

4 Your Ability to Recover from Failure

"Failing forward" has become something of a catchphrase in professional circles, and with good reason. A candidate's ability to recover and learn from failure not only develops their professional capability, but serves to assist the growth and development of those they work with by communicating those lessons to their co-workers.

Almost every interviewer will inquire about a time you failed to achieve something, or a situation in which your skills were not equal to the problem. Answer this question honestly and be prepared to discuss the subsequent results. Think very carefully about what you learned from the situation, and if it prompted you to further develop your skills in a particular area. Demonstrating that failure prompts you to work harder and smarter can help you secure a position.

5 Your Ability to Be a Team Player

While some people work best alone—and you should say so if this is the case—learning to work as part of a team is still a critically important skill, particularly with regard to high-stakes or large projects.

Be prepared to answer questions about times you worked as part of a team, and what you contributed to the team or project you were assigned to. Talk about how your skills complemented those of other team members, and what you were able to achieve together versus what you were able to achieve on your own.

About the Author

Margaret Buj is an interview coach who has helped hundreds of professionals across Europe and the United States get the jobs and promotions they really wanted.

PDA
Parenteral Drug Association

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

The *PDA Letter* and *PDA Journal of Pharmaceutical Science and Technology*

ANDERS JÖNTHER
JAMES AGALLOCO
JAMES AKERS
JAMES COOPER
DENNIS JENKE
MAIK JORNITZ
IRVING PFLUG
JEANNE MOLDENHAUER
KURT BRORSON
MICHAEL MILLER
SUSAN SCHNIEPP

You can too!
Authors wanted

For more information on PDA publishing please visit:

www.pda.org/pdaletter **http://journal.pda.org**

SNAPShot

ATMPs Offer Promise But Also Challenges

Josh Eaton, PDA

Advancements in gene- and cell-based therapies now link the emerging field of advanced therapy medicinal products (ATMPs) to all aspects of the pharma industry. Yet traditional GMP approaches to these products face a multitude of challenges, such as short shelf-lives, specific temperature requirements, facility usage, control strategies, and more. Manufacturers, regulators, and suppliers are all responsible for overcoming these challenges.

In the United States, the US FDA is inundated with data regarding the production of these nascent technologies, although presentation of the data in common terms and conversion of it into knowledge and understanding of the products and processes is lagging. The process for using data to rationalize decisions needs to be integrated with the Quality Risk Management (QRM) process.

The Bioassay Methods Group of the US National Institute of Standards and Technology's Biosystems and Biomaterials Division is working with industry on one specific aspect of this issue: off-target genome editing. Off-target genome editing occurs when a gene therapy modifies genes other than those causing the disease-state of the patient; in other words, genes that are not the "target" of the therapy. Naturally, this introduces the potential for a negative impact, the results of which can be unpredictable. For example, the mistakenly altered genes could result in another ailment, such as dysfunctional enzymes, overreactive hormones, or even cancerous growth of cells. In other cases, the unintended modification may have no repercussions at all. The Bioassay Methods Group is focused on determining the degree of on-target vs. off-target modifications and the subsequent identification, characterization, and evaluation of off-target genome edits and their potential consequences.

Manufacturing operations for advanced therapies can be approached in various ways. Some manufacturers, particularly new companies, may purpose-build a production facility for convenience or out of necessity, while established companies must determine how to reconfigure existing facilities to adapt to these unique products. For instance, a production site may need upgrades to meet particular requirements of a biological product, or a physical plant, while adequate, may operate below capacity due to a decreased volume of production. To compensate, several companies have employed single-use systems alongside, or in place, of conventional stainless steel equipment, a strategy that requires evaluating the possible interactions of the therapeutic product and the raw materials with the disposable equipment—sometimes across several vendors. For autologous therapies, where the starting material is often extremely limited, careful monitoring of materials and processes is crucial, creating a need for increased scrutiny of raw materials and incorporation of process analytical technology to monitor production via inline testing and sampling. Given that many therapies have a limited useful lifetime once produced, the timing of production and the facility's distance from the recipient of the final material are also key factors. Some companies locate their production facilities geographically to account for these concerns; this may require a significant outlay for facility construction and maintenance. Others rely on contract manufacturing organizations (CMOs) for their operations, which brings its own concerns: not all CMOs are equal, so each must be evaluated individually. Depending on the biological product and processes involved—if a specialized technology/skill is required or if any of the materials are toxic or infectious—there may be few viable CMO options.

Not only do manufacturers need to innovate in this area, suppliers will need to adapt. Materials and equipment suppliers, for example, play a critical role in the development of revolutionary treatments for injuries like damaged spinal cords or knee cartilage, and for diseases like Parkinson's and multiple sclerosis. Cell-free manufacturing systems employing GMP-compliant processes are being developed to avoid potential endogenous viral contamination and meet regulatory guidelines. Some innovative suppliers are offering microsized bioreactors capable of producing a single autologous cell therapy dose to avoid cross-contamination and drastically reduce the footprint needed to produce the treatment. Others are envisioning a dehydrated, portable "cell factory" with all components included for on-demand biomolecular manufacturing.

In the rapidly evolving arena of gene and cell therapies, there are many moving pieces and, as part of its mission, PDA intends to aid its members in navigating this ever-changing landscape. Volunteer groups are currently working to revise *Technical Report No. 42: Process Validation for Protein Manufacturing* to reflect the advent of ATMPs and are drafting a new technical report focused on control strategies for producing autologous cell therapies. Both are scheduled for peer review soon.

PDA is sponsoring several events in 2017 that will focus on gene and cell therapies: a workshop following the *2017 PDA Annual Meeting* in April; the annual PDA Europe *Advanced Therapy Medicinal Products* conference in June; and a US-based meeting on ATMPs in December, PDA's first US conference on the topic. PDA has designed these conferences and technical reports to help ATMP manufacturers, regulators, and suppliers address the challenges of these innovative products.

SNAPShot

Journal *Top Ten*

The Latest Industry Research Comprises Half of the Most Popular Journal Articles for February

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

1. PQRI Special Section – *Research*
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

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

3. PQRI Special Section – *Review*
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

4. Research
Marcel Goverde, Julian Willrodt, and Alexandra Staerk, "Evaluation of the Recovery Rate of Different Swabs for Microbial Environmental Monitoring" January/February 2017

5. Research
Roland Guinet, et al., "Multicenter Study on Incubation Conditions for Environmental Monitoring and Aseptic Process Simulation" January/February 2017

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

7. Research
Steven J. Novick, Wei Zhao, and Harry Yang, "Setting Alert and Action Limits in the Presence of Significant Amount of Censoring in Data" January/February 2017

8. Research
Tobias Werk, et al., "A Method To Determine the Kinetics of Solute Mixing in Liquid/Liquid Formulation Dual-Chamber Syringes" January/February 2017

9. Research
Bryan Lei Yu, et al., "Kinetic Modeling of the Release of Ethylene Oxide from Sterilized Plastic Containers and its Interaction with Monoclonal Antibodies" January/February 2017

10. Technology/Application
Kiyoshi Fujimori, Hans Lee, Joseph Phillips, and Yasser Nashed-Samuel, "Development of Conductivity Method as an Alternative to Titration for Hydrolytic Resistance Testing Used for Evaluation of Glass Vials Used in Pharmaceutical Industry" January/February 2017

Validation for Automated Washing Systems

Aaron Mertens, Paul Lopolito, Olivier Van Houtte, and Marcel Dion, Steris

The 2011 US FDA guidance document divides process validation activities into three stages: process design, process qualification, and continued process verification ***(1).*** This lifecycle approach incorporates recommendations from ICH, particularly Q8, Q9, and Q10 ***(2–4),*** and standardizes manufacturing and cleaning processes.

In the lifecycle approach, there is more emphasis on the design and monitoring stages of the process, including understanding critical cleaning process parameters (CCPPs) and defining critical cleaning quality attributes (CCQAs) for the cleaning process. The increased emphasis on continuous process verification ensures the process operates in a state of control. Those monitoring may choose to use process analytical technology (PAT) to record and process data in a timely manner ***(5).***

Figure 1 depicts the lifecycle approach as it relates to traditional markers for sourcing an automated washer for cleaning parts using a validated cleaning process ***(6).***

Stage 1: Cleaning Process Design

A validation strategy and cleaning validation master plan are essential. Both should include details on cycle development, selection of cleaning agents, analytical and sampling methods, acceptance criteria calculations, handling and storage procedures for cleaned components, and cleaning equipment validation.

For new equipment installation—often the case with automated parts washer cleaning validation—the equipment user requirement specifications (URS), functional specifications (FS), and design specifications (DS) are important for successfully commissioning and validating the equipment.

As an example, **Table 1** captures vital information, including part description, item quantity, item dimensions, and specific washing requirements, such as soil and soil condition, and material of construction. The information also includes a drawing that helps in the description of the items.

Stage 2: Process Qualification

Stage 2 is a readiness check which includes qualification of the equipment and cleaning validation process. As a prerequisite to the performance qualification (PQ) or cleaning validation of the automated parts washer, the following items should be considered:

- Approved cleaning protocols and procedures
- Trained personnel
- Qualified utility supply systems

Table 1 Parts Information Table

Item #	Description	QTY	Height (mm)	Out. Dia. (mm)	Weight (kg)	Critical Information	Drawing Number or Picture Number	Notes/ Questions
1	Filling needle	8	110	15	NA	Process soil: Low concentration protein, material: 316LSS		photo 28
2	Filling pump	8	174.5 for pump 150 for plunger	pump out dia. 70.6 Plunger inner dia. 18	NA	Process soil: Low concentration protein, material: External is 316LSS, pump internal is procelaine, can seperate wash		photo 29
3	Glass bottle	1	300	180	NA	Process soil: Low concentration protein, material: glass		photo 30

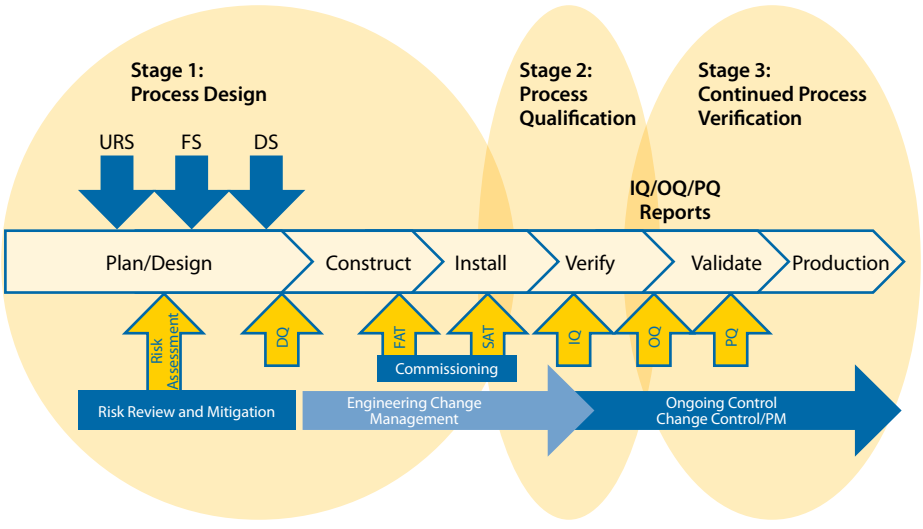


Figure 1 Lifecycle Approach Chart

- Validated analytical methods and sampling procedures
- Approved cleaning agent suppliers
- Fully functional automated washer equipment

Washer qualification consists of Installation Qualification (IQ) and Operation Qualification (OQ). This confirms that the equipment is installed as specified and utilities are sufficient to maintain operation as expected. The procedures include riboflavin coverage testing, successful runs of a complete cleaning wash cycle and verification that all alarms are functioning properly and that sensors/probes are calibrated and functioning as designed.

The cleaning validation, or PQ, of the washer includes sampling of the soiled ➤

The Parenteral Drug Association presents...

2017 PDA Container Closure, Devices and Delivery Systems: Compatibility and Material Safety Workshop

May 8-9, 2017 | Washington, DC

Omni Shoreham Hotel

Exhibition: May 8-9

#2017CC

Co-sponsored by

PQRI Product Quality Research Institute

The world of combination products continues to expand in the world of biologic medicine. Are you prepared for the future of delivery devices?

At the *2017 PDA Container Closure, Devices and Delivery Systems: Compatibility and Material Safety Workshop,* **May 8-9,** gain knowledge and find solutions for issues related to material compatibility and safety for container closure for devices and delivery systems. Join industry and regulatory experts in a forum designed to promote open dialogue on key topics in this evolving field, focusing on various aspects of the lifecycle of drug products and devices.

Discussion will center on:

- Challenges Associated with Qualifying System Platforms and Lifecycle Management
- Particles and Devices
- Strategies for Biocompatibility Testing
- Drug Product Compatibility
- Safety Assessment
- Leachables and Extractables
- Container Closure Integrity
- Supply Chain Supplier Responsibility

Regulatory considerations and industry best practices will also be addressed throughout the Workshop.

To learn more and register, please visit www.pda.org/2017CC

parts to establish a baseline, as well as evaluating the cleaned items (such as visual inspection, rinse or swab sampling) to demonstrate that the final rinse water acceptance criteria corresponds to the cleanliness of the parts washed.

The traditional cleaning validation approach of evaluating multiple runs may be optimized based on the testing performed during Stage 1, based on the design and risk assessment. The requirement to evaluate worst-case critical parameters may not be applicable if the critical parameters identified during the design stage are monitored and controlled during routine operation. The goal of the PQ is to demonstrate that the normal operating cleaning cycle using the automated parts washer successfully removes the residue(s) of interest to predetermined acceptable levels.

The cleaning validation process, including assessing deviation risks, changes, or out-of-specification (OOS) events, should be documented and approved.

Stage 3: Continued Process Verification

For an automated washing system, continued process verification relies on the analysis of the measured CCPPs and CCQAs, such as on-line conductivity and total organic carbon (TOC) of the final rinse water and items such as drying temperature/time and ramp rates which increase cycle times ***(7–8).*** A multiparameter analyzer/transmitter and TOC sensor could be integrated into the washer piping system to determine TOC concentrations in the final rinse water sample. The analyzer/transmitter is connected to the washer programmable logic controller (PLC) for trending the data. Trending data helps support corrective actions prior to development of OOS results, or deviations which can compromise the quality or release of products.

Change control that emphasizes understanding and continuous verification of the cleaning process allows for improvements, reducing production costs while maintaining high quality standards. **Table 2** lists changes to the cleaning process and possible impact as a result of the change ***(9).***

Conclusion

The *cleaning lifecycle approach* moves the emphasis from validation to design and monitoring of the cleaning process. An improved understanding of the design process (critical parameters and URS of the automated parts washer) and continued verification of the cleaning process promotes process improvement and scientific based resolution to OOS results, resulting in more efficient and effective change management. Industry tools such as Quality by Design and risk management provide the backbone to the *lifecycle approach* and how this approach can be incorporated into cleaning validation when using automated parts washers.

[Editor's Note: This article was originally presented as a poster at the *11th Annual PDA Global Conference on Pharmaceutical Microbiology*.**]**

Table 2 Impact of Modifying CQAs

Changes to	May Impact
Detergent	Cleanability of the soils
Cleaning Paramaters	Cleanability of the soils
Analytical Method	Detectibility and quantification of residues
Equipment Design	Surface coverage, equipment drainability, change over time
Personnel	Training and level of experience
Dirty Hold Time	Cleanability of the soils, levels of bioburden
Cleaning Hold Time	Extraneous matter, bioburden

References

1. United States Food and Drug Administration. *Process Validation: General Principles and practices.* November (2011).
2. US Food and Drug Administration. *Guidance for industry: Q8 pharmaceutical development.* May 2006.
3. US Food and Drug Administration. *Guidance for industry: Q9 quality risk management.* June 2006.
4. US Food and Drug Administration. *Guidance for industry: Q10 quality systems approach to pharmaceutical cGMP regulations.* September 2006.
5. United States Food and Drug Administration. *Guide for Industry: PAT – A Framework for innovative pharmaceutical development, manufacturing, and quality assurance.* September 2004
6. Hofacre, M. "Technical Report No. 48. Moist Heat Sterilizer Systems: Design, Commissioning, Operation, Qualification, and Maintenance." Presented at the PDA New England Chapter Spring Meeting, May 11, 2011
7. Dion, M., Van Houtte, O. and Verghese, G., "On-Line TOC Monitoring in GMP Parts Washers" *Pharmaceutical Engineering* (2014): 80–87.
8. Bader, K., Hyde, J., Watler, P., and Lane, A. "On-line total organic carbon (TOC) as a process analytical technology for cleaning validation risk management." *Pharmaceutical Engineering* (2009) 8–20.
9. Lopolito, P and Rivera, E. "*Cleaning Validation: Process Life Cycle Approach*. In *Contamination Control in Healthcare Product Manufacturing Volume 3*, edited by Madsen, R., and Moldenhauer, J. 285–339. Bethesda, MD: PDA/DHI. 2014.

About the Authors

Aaron Mertens has been a member of the STERIS Life Sciences Contamination Control Solutions Technical Service Group as a Technical Service Specialist since January 2015. In this role, he has responsibility for providing global technical support primarily for critical environments, sterility assurance and barrier products, application and validation.

Paul Lopolito is a senior technical services manager for the Life Sciences Division of STERIS Corporation. He currently provides global technical support related to process cleaning and contamination control.

Olivier Van Houtte is Product Manager in the Life Sciences Division of STERIS Corporation.

Marcel Dion is Director of Marketing for Washing and Steam Sterilization Systems in the Life Sciences Division of STERIS Corporation.

Find the perfect audience for your company's products and services at two upcoming PDA events!

2017 PDA Quality Risk Management for Manufacturing Systems Workshop

June 19-20, 2017 | Chicago, IL

Hyatt Centric Chicago Magnificent Mile

Exhibition: June 19-20

#2017QRM

Photo courtesy of Sartorius AG

The *2017 PDA Quality Risk Management for Manufacturing Systems Workshop* will inform attendees about the need for and how to integrate risk-based thinking into evolving manufacturing systems.

Meet attendees during breaks and the Networking Reception. Share how your company is aligned with and can help them address new developments and innovations in the field.

2017 PDA Biosimilars Conference

June 26-27, 2017 | Bethesda, MD

Hyatt Regency Bethesda

Exhibition: June 26-27

#2017Bio

Good foot traffic is one thing; great leads are another. At the *2017 Biosimilars Conference*, you will have access to attendees from a variety of manufacturing companies, all of whom are looking for solutions and strategies to successfully bring biosimilars to market.

Don't let these cost-effective exhibit/sponsorship opportunities pass you by!

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

2017 PDA Upcoming Events

SAVE THE DATE for PDA's 2017 Events

APRIL

18-20
Airflow Visualization Techniques and Practices
Bethesda, MD
pda.org/2017AprAir

18-21
Regulatory and Compliance Course Series
Bethesda, MD
pda.org/2017RCS

26-27
Current Trends in Aseptic Fill & Finish of Pre-filled Syringes Conference
Lindau, Germany
pda.org/EU/FillFinish2017

MAY

1-4
Fundamentals of Aseptic Processing
Bethesda, MD
pda.org/2017FundAPT

3-4
Basics of Successful Auditing
Berlin, Germany
pda.org/EU/Auditing2017

8-9
2017 PDA Container Closure, Devices and Delivery Systems: Compatibility and Material Safety
Washington, DC
pda.org/2017CC

10
2017 PDA Pre-filled Syringe Interest Group Meeting
Bethesda, MD
pda.org/2017PFS

11
2017 PDA Combination Products Interest Group Meeting
Bethesda, MD
pda.org/2017Combo

12
Technical and Regulatory Challenges of Drug Delivery Combination Products – Pre-filled Syringes, Autoinjectors and Injection Pens
Bethesda, MD
pda.org/2017TRC

15-19
PDA #100 Aseptic Processing Option 3 Week 2: Jun. 12-16
Bethesda, MD
pda.org/2017Aseptic3

22-25
Lyophilization Course Series
Bethesda, MD
pda.org/2017Lyo

23-24
Single Use Systems for the Manufacturing of Parenteral Products
Bethesda, MD
pda.org/2017SUS

29
The Principles of Viral Safety for Biologics and Vaccines
Dubrovnik, Croatia
pda.org/EU/Pre-WS-Viral2017

30-1
Virus & TSE Safety Forum
Dubrovnik, Croatia
pda.org/EU/Virus2017

31-2
Validation of Moist Heat Sterilization Processes
Bethesda, MD
pda.org/2017MayMH

JUNE

2
Virus Filtration
Dubrovnik, Croatia
pda.org/EU/Virus-Filtration2017

6-7
Isolator Technology
Bethesda, MD
pda.org/2017IT

12
Cleaning and Disinfection
Berlin, Germany
pda.org/EU/CD2017

12
Quality by Design for Biopharmaceuticals
Berlin, Germany
pda.org/EU/QBD2017

12
Supply Chain Strategies for API and Drug Products
Berlin, Germany
pda.org/EU/SupplyChain-API2017

13-14
2nd PDA Europe Annual Meeting
Berlin, Germany
pda.org/EU/Annual2017

Denotes Laboratory Courses | Denotes Lecture Courses

PDA
Parenteral Drug Association

For an updated PDA calendar of events, please visit:

pda.org/calendar

15-16
Introduction to Aseptic Processing Principles
Berlin, Germany
pda.org/EU/TCAseptic2017

15-16
Quality Culture
Berlin, Germany
pda.org/EU/Quality-Culture2017

19-20
2017 PDA Quality Risk Management for Manufacturing Systems Workshop
Chicago, IL
pda.org/2017QRM

19-22
Biotechnology Course Series
Bethesda, MD
pda.org/2017BCS

20-22
Environmental Monitoring Course Series
Bethesda, MD
pda.org/2017JunEM

26
Practical Application of Phase-Appropriate GMP & Quality to Clinical Development of ATMPs
Valencia, Spain
pda.org/EU/TCATMPs2017

26-27
2017 PDA Biosimilars Conference
Bethesda, MD
pda.org/2017Bio

26-30
Quality Course Series
Bethesda, MD
pda.org/2017QCS

27-28
Advanced Therapy Medicinal Products
Valencia, Spain
pda.org/EU/ATMPs2017

JULY

24-28
PDA #100 Aseptic Processing Option 4
Week 2: Aug. 21-25
Bethesda, MD
pda.org/2017Aseptic4

31-1
Sterile Pharmaceutical Dosage Forms: Basic Principles
Bethesda, MD
pda.org/2017Sterile

AUGUST

2-3
Fundamentals of Cleaning and Disinfectant Programs for Aseptic Manufacturing Facilities
Bethesda, MD
pda.org/2017Clean

8-9
Mold Identification for Quality Control
Bethesda, MD
pda.org/2017QC

9-10
Assessing Packaging and Processing Extractables/Leachables
Bethesda, MD
pda.org/2017APP

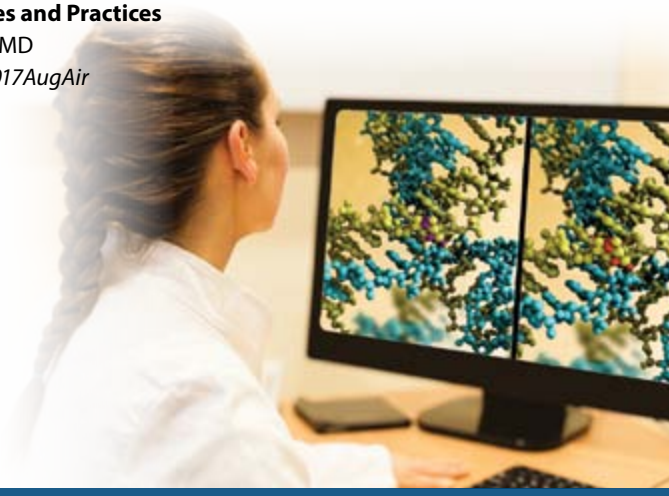
15-17
Airflow Visualization Techniques and Practices
Bethesda, MD
pda.org/2017AugAir

Stay engaged, informed and ahead of the complex challenges of the bio/pharmaceutical manufacturing world by following PDA on:

Twitter at **@PDAOnline**

LinkedIn at **LinkedIn.com/company/PDA**

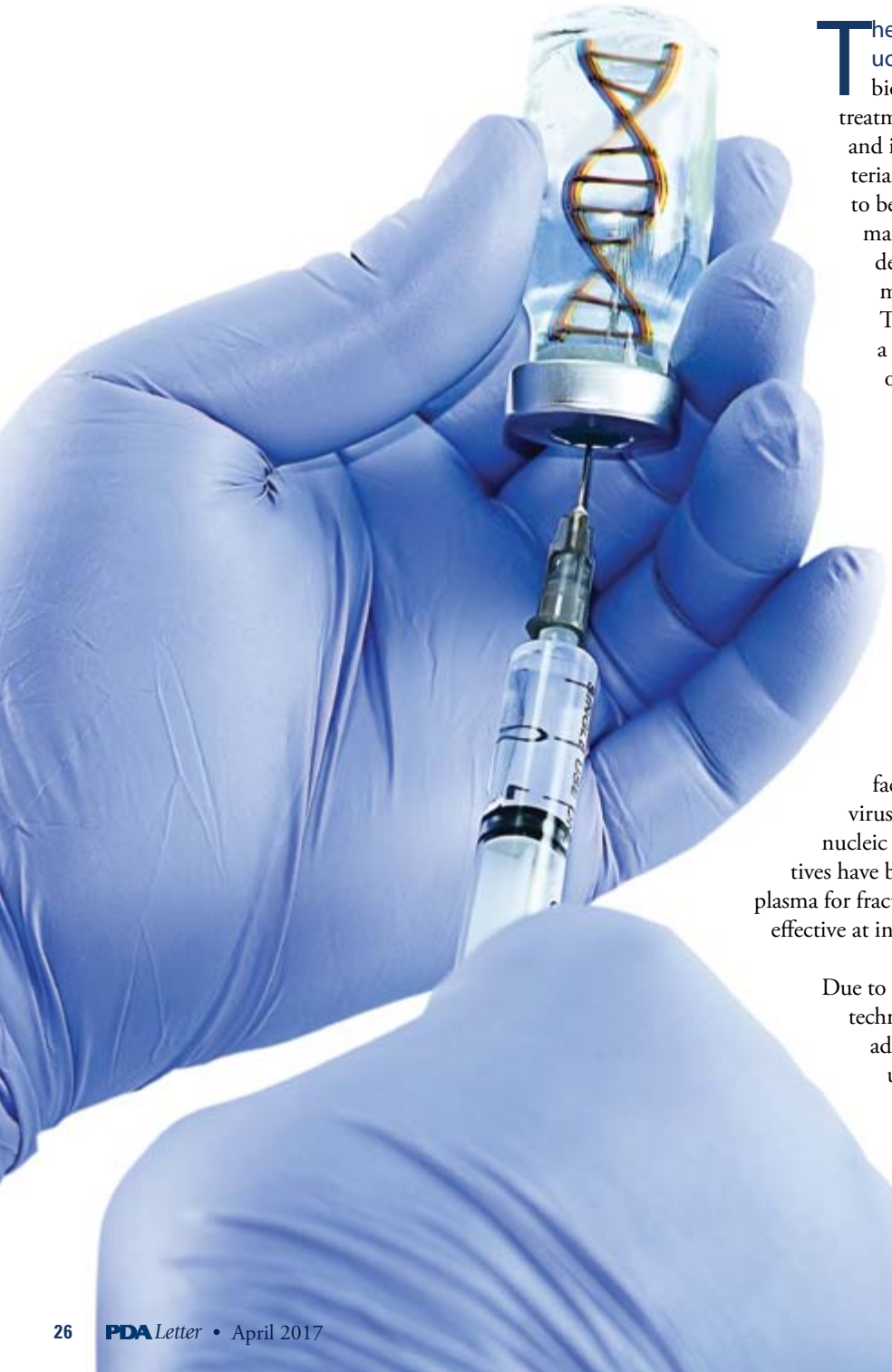
PDA Connect℠ **community.pda.org**
PDA's members-only online discussion forum



2016 Viral Safety of ATMPs Conference

Viral Safety Approaches for Advanced Therapy Medicinal Products

Thomas R. Kreil, PhD, Global Pathogen Safety, Shire



The availability of plasma-derived medicinal products—one of the earliest achievements of medical biotechnology—has enabled great progress in the treatment of specialized conditions such as hemophilia and immune deficiencies. Yet early on, the biologic materials used to develop these products were also found to be vulnerable to infectious disease agents. Today, manufacturers safeguard these products during the development process through a set of measures commonly referred to as the "Safety Tripod" (**Figure 1**). This consists of the *selection* of plasma donors with a low risk of contact to infectious agents, the *testing* of plasma donations for the absence of selected infectious agents and, finally, virus inactivation and removal (=*reduction*) processes. These measures are also required by regulators ***(1).***

With time, it has become clear that the reduction capacity is by far the most significant quantitative contribution to product safety margins (**Figure 1**). For example, since the arrival of West Nile virus in the United States, directly transfused blood product—the safety margins of which depend exclusively on donor selection and donation testing, as they typically do not undergo any virus-reducing manufacturing process—has occasionally transmitted the virus, despite testing using modern and very sensitive nucleic acid-based methods ***(2).*** In contrast, plasma derivatives have been safe, even without West Nile virus testing of plasma for fractionation, as their manufacturing processes are more effective at inactivating or removing the virus ***(3).***

Due to the success of the "Safety Tripod" concept, biotechnology manufacturers of therapeutic proteins have adapted it for their own processes. Arguably, this product class has never been reported to transmit a virus to a recipient, yet contamination of manufacturing platforms has occurred. As to the specific interventions applied to ultimately enhance product safety margins, a careful *selection* process is used to minimize any risk of exposure

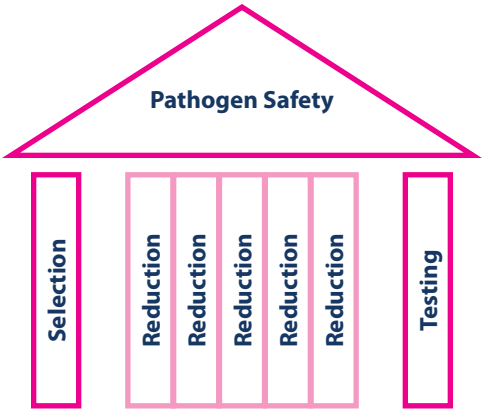


Figure 1 Safety Tripod

to an infectious agent for the production cell line as well as for raw materials entering the manufacturing process. The chosen cell banks as well as individual fermenter harvests are subject to *testing* to ensure the absence of infectious agents. And finally, virus *reduction* processes are implemented into the downstream purification process for biotechnology products.

Now, advanced therapy medicinal products (ATMPs) are entering the market, offering potential advancements for maintaining and improving human health, just as plasma-derived medicinal products did in the mid-20th century. ATMPs face the same contamination threats from exposure to universally present and effective opportunistic agents in the microbiological environment as traditional biologics. In recent years, the manufacturing platform of an already licensed ATMP was found to be contaminated with a virus, fortunately one not pathogenic to humans ***(4).*** This led the manufacturer to add a nanofiltration step for this product, following recommendations for a virus reduction method.

Therefore, it is important to embrace the safety concepts that have been so effective in protecting more traditional biotechnol- ➤

Article at a Glance

- ATMPs face similar virus safety threats as traditional biologics
- Virus reduction barriers more successful upstream
- Regulators now developing guidance in this area

> **ATMPs face the same contamination threats from exposure to universally present and effective opportunistic agents**

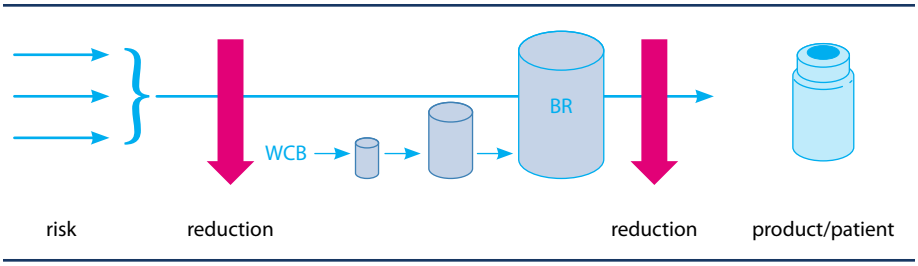


Figure 2 Upstream versus Downstream Virus Barrier

ogy products. With ATMPs, this begs the question—how can this technically be accomplished?

Manufacturers Swim Upstream

The selection and testing procedures used in biotechnology have at times failed the expectations placed in them. Fortunately, this situation is expected to improve as testing becomes as innovative as the end product itself. Take next-generation sequencing, for example. This technique is now being used increasingly during characterization of cell banks. It establishes the absence of adventitious agents without any prior knowledge about them. But advances in virus reduction processes offer a more solid solution. While options for virus reduction may be limited, they do exist. A publication from the German Paul-Ehrlich-Institute showed that Adeno-associated virus (AAV) gene therapy vectors can be treated with solvent-detergent (SD) combinations to inactivate any lipid-enveloped adventitious viruses. This has no impact on the nonlipid enveloped therapeutic entity; furthermore, larger pore size nanofilters can remove large adventitious viruses with effective passage of the very small AAV ***(5).***

Even more innovatively, any risk associated with the starting material of a biotechnology process can also be separated from the final product, and, ultimately, the patient, by a virus reduction barrier placed upstream rather than the traditional downstream (**Figure 2**). In fact, for ATMPs, such as large lipid-enveloped virus gene therapy vectors and similar cell-based therapies, it may not be possible to apply virus reduction technologies to the product or production intermediate containing the active drug substance. Thus, ensuring viral safety of all raw materials used in cell culture is highly important and applying virus reduction methods at the raw material level significantly diminishes the contamination risk for cell cultures. An upstream intervention may be the only technically feasible means of providing virus reduction capacity within the manufacturing process. More importantly, an upstream barrier approach not only offers additional safety margins for the final product but also protects the fermenter from exposure to an infectious agent. Otherwise, any minimal inoculum might result in exponential amplification of the agent, potentially to titers that may even overwhelm any downstream virus reduction capacity. In addition, maintaining the integrity of the manufacturing setting by avoiding any exposure results in an uncompromised ability to serve the patients waiting for the respective medicinal product.

With technological progress in the ATMP space so incredibly rapid in recent years, regulators are now establishing or refining procedures to convey these products to market ***(6).*** The pathogen safety concepts reflected in regulatory guidance documents do recognize some of the technical limitations ("possibilities for applying virus clearance steps … are limited"), yet sound conceptually very familiar ("selection and control of starting materials (including seed and cell banks), raw materials...application of vector purification process steps which, where feasible, provide elimination/inactivation capacities vis-a-vis relevant viruses") ***(6).***

It is exciting to see how top science is being brought to fruition in a public health setting so quickly. With all the focus on innovation, however, it is equally important not to forget the lessons of the past, and to use available biomanufacturing tools to safeguard these modern biomedicines along the lines of proven concepts.

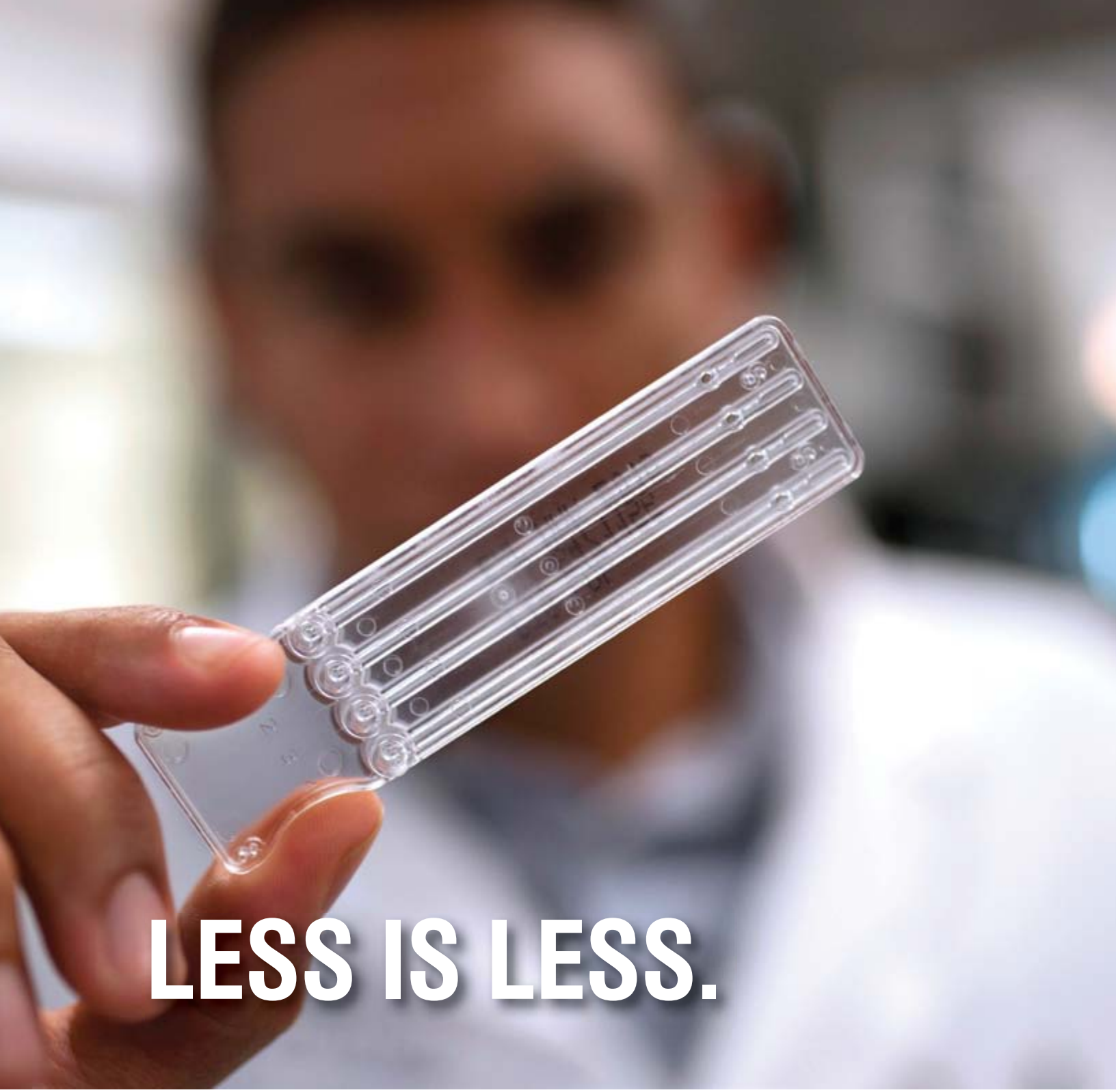
[Editor's Note: This article is based on the author's presentation delivered at PDA's 2016 *Viral Safety of ATMPs* conference in Berlin**.]**

References

1. Guideline on plasma-derived medicinal products, EMA, 2011, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/07/WC500109627.pdf
2. Montgomery, S.P., et al. "Transfusion-associated transmission of West Nile virus, United States 2003 through 2005." *Transfusion* 46 (2006): 2038–2046.
3. Kreil, T.R., Berting, A., Kistner, O. and Kindermann, J. "West Nile virus and the safety of plasma derivatives: verification of high safety margins, and the validity of predictions based on model virus data." *Transfusion* 43 (2003): 1023–1028.
4. Ma, H., et al. "Identification of a novel rhabdovirus in Spodoptera frugiperda cell lines." *Journal of Virology* 88 (2014): 6576–6585.
5. Stuehler, A., and Bluemel, J. "Viral Safety of Biological Drugs." *Federal Health Gazette* 57 (2014) 1198–1202.
6. Draft guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products, EMA, March 23, 2015 www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/05/WC500187020.pdf

About the Author

Thomas R. Kreil, PhD, is Senior Director of Global Pathogen Safety at Shire. He has contributed to the field of pathogen safety for vaccines as well as plasma-derived, biotech and ATMPs for almost two decades.



We've refined our FDA-licensed PTS™ cartridges to require 20 times less raw material than conventional assays, so that responsibility, rather than demand, can continue to guide our operations. Continuing our commitment to conservation, this technology allows us to support humane practices and optimize our resources while reducing the impact on horseshoe crab populations. Gain immediate access to LAL and reliably test for endotoxins in just 15 minutes – ultimately decreasing investigations, variability and retests.

Discover how to do more with less at www.criver.com/nexgen-PTS.

2016 Advanced Therapy Medicinal Products Conference

How to Get Your ATMP From the Lab to the Market

Andy Fry, Team Consulting

What is actually involved in taking an advanced therapy medicinal product (ATMP) from a brilliant idea in the lab to a successful product on the market? Is it similar to the development of a combination product? Or a monoclonal antibody? Just how difficult can it be? The level of activity surrounding ATMPs has been increasing, with some remarkable therapeutic opportunities currently being explored.

First, let me begin with a definition: "advanced therapy medicinal products" (or ATMPs) is a regulatory term used in Europe for medical products based on genes (gene therapies), cells (cell therapies), and tissues (tissue engineering). "Regenerative medicine" is another often-heard term that describes a similar range of products. ATMPs are complex and diverse, with varying requirements, both for manufacturing and delivery. Cells are living entities, and a comparison with biologics can be misleading; human DNA has a molecular weight of 2.2 TDa, i.e., 15×10^6 × the molecular weight of adalimumab (Humira®), which alters our view of delivery options.

Getting to a Realized Product

For an ATMP product to be successful, the No. 1 usual requirement is that it be clinically effective, meaning the clinical outcome results in a measurable improvement in the patient's condition. Equally important future matters need to be considered, however. How will the product or therapy actually be applied or delivered? Who will deliver or administer the therapy? What form could any delivery device or system take? There are more questions when it comes to manufacturing. How could it be manufactured? What are the GMP implications and considerations? What should the objectives be regarding capability/robustness of the design? And the bottom line: what will the cost of goods be—and do we understand what the market acceptable price is likely to be?

Rational, objective answers to these questions must be based on more than a rose-tinted dream of what a "great idea" or "clever science" can achieve. While I do not want to pour cold water on the promise offered by any brilliant/innovative science, serious consideration of the practical means of manufacturing and applying the product or device is equally important.

First, let me acknowledge that innovation is a creative process, of which individual genius, the creative spark, and eureka moments are just initial steps. But the questions of "How do we make it?" and "How will it be delivered?" are as essential to this process as the science. See **Figure 1** for an example of what happened when one company prioritized the initial innovation over the process.

Teamwork, Teamwork, Teamwork

The nature of ATMPs and regenerative medicines demands bringing deep biological knowledge and complex engineering skills to the development team ***(1).*** This blending of skillsets is difficult to achieve but necessary for any organization to succeed. To bring ideas from the lab bench to commercial reality requires engineers and designers who understand biology and clinical science as well as biologists and clinical scientists who understand engineering and design ***(2).*** Team members must be willing to share, engage, and respect each other across the spread of disciplines and skills. An Innovation Management approach (already proven across a wide range of sectors), embraces a mindset and guiding philosophy that suits ATMP development extremely well. As applied within my own organization, Innovation Management describes a healthy mix of attributes and inputs from the overall development team: *creativity* (freedom to explore, develop, and suggest new ideas), *science and supportive/explanatory theory* (ability to understand and validate concepts and potential solutions), and *structural formality* (procedures for capturing actual achievement and focusing on shared goals and objectives).

It is important to recognize that all these attributes and inputs—creativity, science, and structure—need to be present throughout the development process, but the ratios will vary as development progresses. At the front end, plenty of creativity, backed by enough science (and a light touch of structure) and theory, helps pick out promising approaches and close down dead ends. Later stages demand a lot of structure, informed by sound theory for validation, with more limited opportunity for creativity.

Three Critical Attributes Necessary

Clinical efficacy starts the process. The next steps for a successful product are usability and manufacturability. For ATMPs, unless all three attributes are taken seriously, a therapy may be, at best, suboptimal—or, at worst, a disaster.

Usability, its assessment and improvement, is the primary objective of human factors engineering. Put simply, it's about making sure that a product, device, or system is easy to use correctly and difficult to use incorrectly. Standards and guidance documents for analytical and empirical human factors engineering include ISO 62366, ANSI/AAMI HE75, and the US FDA's guidance, *Applying Human Factors and Usability Engineering to Medical Devices*. Human factors engineering should

Figure 1 ATMP – cell-cultured skin | www.alamy.com

A cell-cultured skin was developed by a US company in 1997, a brilliant achievement from a scientific viewpoint—a highly effective answer to an unmet need for diabetic foot ulcers and venous leg ulcers. But the math didn't add up: the cost to produce, package, distribute, and apply the cultured skin to the patient was well above the cost threshold for payers. The company could not make the product profitable and filed for bankruptcy in 2002.

The happy ending to this story is that the company relaunched in 2003 and is now profitable.

ELIMINATE PARTICULATES & FIBERS IN THE CORE.

SYNTHETIC WRITING SUBSTRATE

CleanPrint 10

- Low particulate and non-shedding
- Exceptionally durable
- Abrasion and chemical resistant
- Easy to write on
- Double bagged packaged sterile

CUSTOM DOCUMENTATION

Core 2 Write

- Logbooks, ID tags, Forms and Labels
- Constructed using CLEANPRINT 10
- Customized specifically per customer
- Individual unique numbering and integrity features
- RFID Technology available

HEPA FILTERED PRINTING SYSTEM

Core 2 Print

- Print wirelessly into cleanrooms
- Use with pre-sterilized CLEANPRINT 10
- 316L Stainless Steel Construction, can be completely disinfected
- HEPA Filter cabinet
- Sheet fed, high speed digital printer using chemical resistant ink

vai
VELTEK ASSOCIATES, INC.

15 Lee Boulevard
Malvern, PA 19355-1234 USA
(610) 644-8335

www.sterile.com

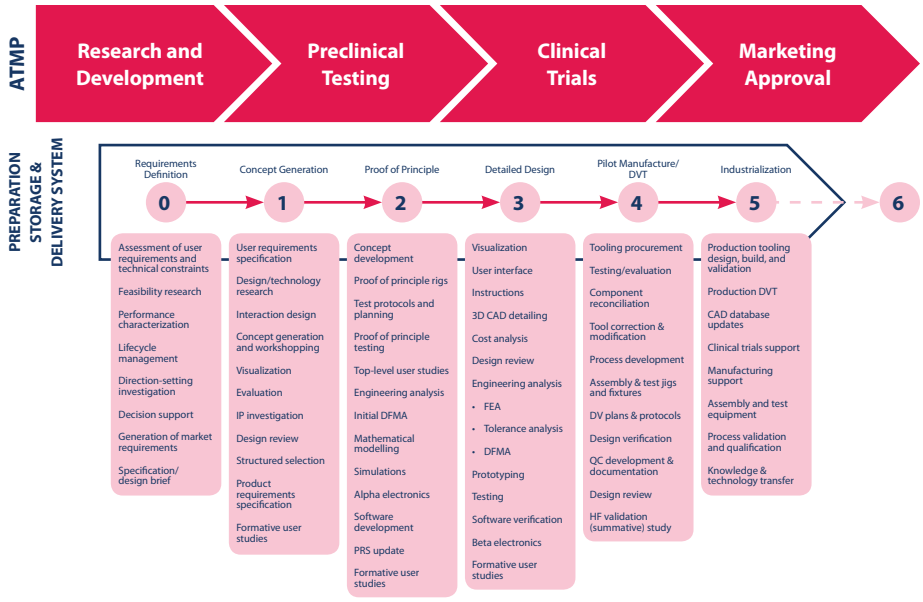


Figure 2 Device Development Process as Applied to ATMPs

Figure 3 DNA Vaccination System | www.cartoonstock.com

A potentially promising DNA vaccine was offered with a very hard-to-use delivery system, requiring exceptional strength and dexterity in use. Despite potential therapeutic benefit, the delivery system discouraged users and was unsuccessful in its original form. Reputational damage is not easily undone, irrespective of the potential of the therapy itself.

inspire and inform innovation and design.

Manufacturing is often the forgotten guest, invited in when the celebrations have come to a halt because no one remembered to bring a corkscrew! ATMPs often require developing new tools, techniques, and processes, and the initial vision of the new therapy has to acknowledge that process engineering, GMPs, device engineering, and regulations are as crucial as good science. Clarity on several key matters must be achieved early on, such as who will be responsible for design and manufacturing and how will the product be packaged, sterilized, and shipped? I recommend also looking at processes and techniques from different industries (e.g., food, electronics, automotive, etc.) from a GMP perspective.

A couple of final words regarding both usability and manufacturing. There is no shame in requesting expert help; a great deal can be gained from early engagement with "outsiders" in human factors engineering, manufacture, and design. Usability and manufacturability are *not* something that can be ignored until the end of development.

Most ATMPs begin existence in the lab, using manual methods and protocols. It can be expected that human variability may conceal either latent weakness or potential promise, especially as the development progresses. Early, critical, and objective assessment of the status of the product and what has been achieved is essential. Technology Readiness Levels were originally used in the defense industries to judge the development status of weapons systems and aircraft. They are equally valid in assessing the true status of medical development projects (**Table 1**). The "valley of death" defines the transition from proof of concept to proven capability in manufacture and ensures stakeholders share a common appreciation of what challenges have been met and where resources need to be applied.

It can also prove very useful to apply some early, simplified automation steps to help screen out erroneous effects. It's human nature to nurse our pet projects through the lab, such that real performance potential or issues are never observed. Simple, "manumatic" streamlining of processes can help set the template for later development stages.

The Development Process for ATMPs

The ideal point to begin considering

Table 1 Technology Readiness Levels

TRL 4 – 7
"The Valley of Death"

TRL 1	TRL 2	TRL 3	TRL 4	TRL 5	TRL 6	TRL 7	TRL 8	TRL 9
Basic Idea	Concept developed	Experimental proof of concept	Process validation in a laboratory	Process validated on production equipment	Process validated on production equipment	Capability validated on economic runs	Capability validated over range of parts	Capability validated on full range of parts over long periods
Basic research		Preclinical research		Late preclinical research	Phase I trials	Phase II trials	Phase III trials	Phase IV trials
Research		Translation/Development				Commercialization		

manufacture, storage, and delivery is during, or even before, preclinical testing. It becomes very difficult, time-consuming, and expensive to make changes once clinical testing is underway. **Figure 2** shows a typical device development process overlaid against the ATMP development process (transition from TRL 3-4 falls within Stage 2, Proof of Principle; transition from TRL 6-7 falls within Pilot Manufacture/DVT, Stage 4).

It makes no sense to delay consideration of the manufacturing process and delivery method, since these aspects often define the ATMP. Without early consideration of design, engineering, and manufacture of the product and means of delivery, an ATMP may never emerge as a product, commercially or therapeutically, as shown in **Figure 3.**

Though ATMP development processes differ from those for production and delivery systems, success depends substantially on the latter.

The wide variety of therapy types, delivery/application requirements, and manufacturing processes often means there is a very limited scope for making use of off-the-shelf production and delivery solutions. Furthermore, clinical trials usually look very different to those for pharma products, especially as ATMPs may be produced in very small batches (possibly down to n=1).

Conclusion

Innovative science, product engineering, and commercial imperatives must all be integrated to achieve a successful ATMP. The harsh realities of bringing a breakthrough ATMP to the market won't go away if we ignore them—we will just experience failure and lost opportunity. Assessing the clinical benefit of a potential ATMP must be accompanied by more intelligent product development focused on improved manufacture.

The wisdom of involving all stakeholders early on should be obvious. If we ignore the role each stakeholder plays, the outcome will suffer. Improving our ability to judge objectively the clinical, technical, and commercial potential of a great idea has to be beneficial to the development process and to those involved. A range of applicable tools and techniques are available. But these tools sit alongside more fundamental characteristics of proven value in development and working as a team—honesty, thoroughness, technical rigor...and now and again, a touch of humility, since none of us know all the answers!

[Editor's Note: The author presented this at last year's PDA ATMP conference in Berlin**.]**

*Acknowledgements to **Richard Archer** of TwoBC Ltd, and to **Ben Wicks** and **Vicky Shipton** at Team Consulting*

Continued at bottom of page 45

GMP Cycle for an Autologous Cell Therapy

The Parenteral Drug Association presents:

PDA Europe Exchange Series 09/17

Meet, Exchange and Connect

Particles in Injectables

10th Workshop of Monoclonals Antibodies

Register by 30 July 2017 and SAVE!

26-27 September 2017

Hotel Sofitel Berlin

Berlin | Germany

pda.org/eu/particles2017
pda.org/eu-monoclonals2017

The Parenteral Drug Association presents the...

2017

PDA/FDA Joint Regulatory Conference

September 11-13, 2017 | Washington, DC

Renaissance Washington, DC Downtown Hotel

EXHIBITION: SEPTEMBER 11-12 | POST WORKSHOP: SEPTEMBER 13-14 | COURSES: SEPTEMBER 14-15

#2017PDAFDA

Register before June 30 and save up to $600!



Ensuring Product Quality in an Era of Innovative Therapies

The *2017 PDA/FDA Joint Regulatory Conference* is the premier pharmaceutical manufacturing event where you can engage directly with U.S. FDA representatives and industry experts! FDA regulators will provide updates on current efforts affecting the development of global regulatory strategies and industry experts will present case studies illustrating how they employ global strategies to improve the quality of medical products.

Through plenary, concurrent, breakfast and interest group sessions, gain new perspectives and best practices on important industry topics, including:

- Product Quality
- Lifecycle Management
- Investigations
- Global Harmonization Initiatives
- Regulatory Challenges and Opportunities
- Manufacturing of the Future with Submissions
- Prescription Drug User Fee Act
- Center and Compliance Updates
- Much more!

Join nearly 1,000 of your peers and engage directly with FDA experts and representatives of global regulatory authorities at this signature event to discover more about the advanced biomedical innovations leading to safer and more effective therapies for patients!

Learn more and register at *pda.org/2017PDAFDA*

PDA Education will also be hosting five courses designed to advance your knowledge. Learn more and register at ***pda.org/2017RCCS***

SNAPShot

PDA Supports Efforts to Encourage Manufacturing Innovation

Ursula Busse, PhD, Novartis

Barriers to innovation during lifecycle management of a product are multiple. They notably include the complexity of the current post-approval change (PAC) regulatory environment. Recognizing the need for action, several international organizations are currently working toward the global convergence of regulatory requirements for PACs.

In 2014, ICH began its work on ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management.* The main objective of ICH Q12 is to facilitate predictable and efficient PAC management in order to support innovation and ensure reliable product supply. PDA launched its Manufacturing Science and Operations Program (MSOP) in 2014 and offered a Manufacturing Science workshop addressing the barriers for implementation of PACs the following year.

Shortly before the workshop, a team of highly motivated PDA volunteers gathered to form a task force and set out to develop a new PDA technical report that would supplement ICH Q12 by offering specific solutions to facilitate innovation and industry collaboration. The task force later expanded its portfolio of planned activities to include other documents covering related topics and tools. New team members joined. And after a face-to-face meeting in January 2016, the task force decided to continue the journey under a new name and program: "Post-Approval Changes: Innovation for Access to Medicines℠," or PAC iAM.

The PAC iAM program has the following objectives:

- **Bring awareness** to current challenges and enable stronger collaboration among opinion leaders and key stakeholders
- **Foster a science- and risk-based approach** to PAC management and regulatory decision-making for global product quality, safety, and efficacy assessments
- **Encourage international convergence/standardization** in PAC management in a manner that can foster and **enable mutual reliance** between regulatory authorities
- **Manage PACs through** the use of **an effective Pharmaceutical Quality System (PQS)**

Last year turned out to be a very busy year for the PAC iAM team. First, the team raised awareness of the issue in a call to action (see October *PDA Letter*, p. 34), inviting the broader pharmaceutical industry and regulatory community to join efforts in tackling the "wicked problem" of drug shortages (see "Drug Shortage is a "Wicked Problem"" by **Anders Vinther** on the *PDA Letter* website).

Members of the task force also authored a series of Points to Consider (PtC) papers on technical product lifecycle management for publication in the *PDA Journal of Pharmaceutical Science and Technology.* The first PtC paper, entitled "Communication and Knowledge Exchange between Marketing Authorization Holders and Health Authorities," was published in January. The second PtC paper, entitled "Pharmaceutical Quality System Effectiveness For Managing Post-Approval Changes," published in February, elaborates on the role of the pharmaceutical quality system (PQS) in supporting effective change management. The paper describes how opportunities outlined in ICH Q10: *Pharmaceutical Quality System* can be used to manage product and process changes within the PQS to reduce regulatory reporting requirements. **[Editor's Note:** See story on p. 9 for links to the articles**.]** A third PtC paper covering Quality Risk Management and knowledge management for PACs is currently in development.

In the fall of 2016, members of the task force formed a team to work on a PAC technical report that focuses on the practical aspects of PAC management using science- and risk-based approaches and illustrates how an effective PQS can support change management. It will be based on best practices across the industry. The technical report team intends to publish examples of Post-Approval Change Management Protocols (PACMPs) that can be used for various manufacturing changes involving a range of product types.

Finally, in December 2016, PDA launched a survey on PACs to collect data on what resources companies expend handling PACs in the current regulatory environment.

In light of all these activities that began in 2016, what is planned for 2017? Apart from the wealth of ongoing activities outlined above, PDA intends to offer a PAC workshop immediately following the *2017 PDA/FDA Joint Regulatory Conference* in September.

PAC iAM has taken us on an exciting journey so far that will surely continue. To learn more about the PDA PAC iAM program, please visit our website: www.pda.org/pac.

WHO Should Align with ICH on PACs

December 16, 2016

Dr. Hye-Na Kang
Department of Essential Medicines and Health Products
World Health Organization
1211 Geneva 27, Switzerland
kangh@who.int

Reference: WHO/PAC for BTPs Draft/3 Oct 2016— Guidelines on procedures and data requirements for changes to approved biotherapeutic products

Dear Dr. Kang,

PDA appreciates the opportunity to comment on this draft guideline and applauds the efforts put forth here by the World Health Organization to align post-approval change expectations across many jurisdictions. This comes at a pivotal time, especially in light of the discussion around postapproval changes and the drafting of ICH Q12 and Pharmaceutical Life Cycle Management. The direction here will surely help worldwide jurisdictions improve, and even avoid, drug supply issues for important biotherapeutic treatments.

PDA recommends this guideline be fully aligned with concepts in ICH Q12 once finalized and with ICH Q10 Annex 1 *'Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches'*. Q10 states that when companies can demonstrate an effective PQS and product and process understanding, including the use of quality risk management principles they 'gain the opportunity to optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement'. Based on this PDA recommends that WHO ensure this guidance allows for leveraging the PQS for moderate changes where there is no increased risk to product quality, safety and/or efficacy by considering management such that implementation can occur unless the regulatory authority provides indication of concern within 30 days.

PDA recognizes that suggested review timelines for major and moderate changes align with the WHO vaccine document. However, biotech products are well characterized and should not require the same duration of review as complex vaccines. PDA therefore suggests that the proposed times in this draft could be shortened.

Finally, the guidance as currently written does not clearly address the post approval regulatory pathway for any improvements in potency assays for biotechnology products. This is a critical gap that should be addressed.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in pharmaceutical and biological manufacturing including members representing the Science Advisory Board, the Regulatory Affairs and Quality Advisory Board, and Board of Directors.

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

Sincerely,
Richard Johnson
President and CEO, PDA
Cc: Denyse Baker, PDA; Richard Levy, PDA

PDA Commenting Task Force

Melissa Seymour, Biogen (Leader)

Ursula Busse, Novartis

Michael De Felippis, Eli Lilly and Company

Karolyn Gale

Emma Ramnarine, Genentech/ Roche

The Parenteral Drug Association presents the...

2017 PDA Pre-filled Syringe Interest Group Meeting

May 10, 2017 | Bethesda, MD

PDA Training and Research Institute

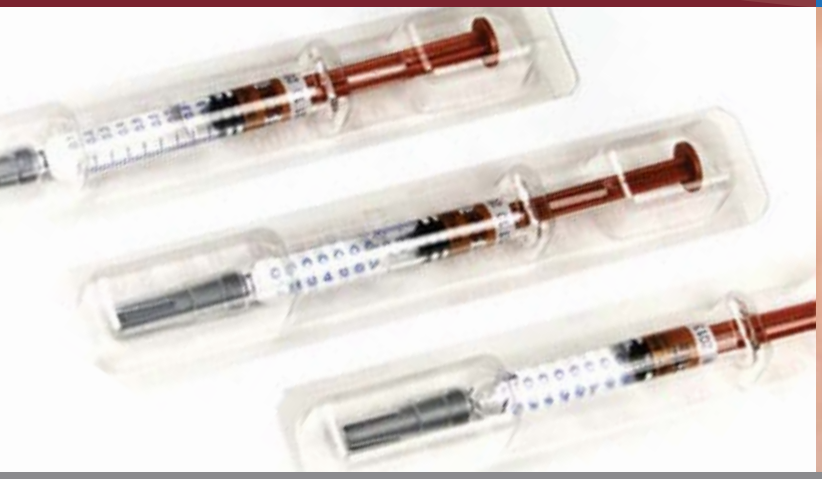
#PDAPFS

2017 PDA Combination Products Interest Group Meeting

May 11, 2017 | Bethesda, MD

PDA Training and Research Institute

#2017Combo



Double your information and networking opportunities with ***back-to-back*** PDA Interest Group meetings! The *2017 PDA Pre-Filled Syringe Interest Group Meeting* will take place **May 10** and the *2017 PDA Combination Products Interest Group Meeting* will take place **May 11** at PDA's newly expanded training facility.

Each one-day, attendee-driven meeting will offer extended discussion with industry experts and peers on related hot topics.

At the *2017 PDA Pre-filled Syringe Interest Group Meeting*, participate in discussions on:

- Silicone Oil: Case Studies
- Quantification & Alternatives to Silicone Oil
- Glass Breakage
- ISO 11040-8

At the *2017 PDA Combination Products Interest Group Meeting*, participate in discussions on:

- Combination Product Quality Systems
- Regulatory Expectations for Combination Products
- Connected Health
- Post-Approval Considerations

To ensure an effective environment for interactive discussions, attendance to each event is limited, so make sure to reserve your spot early by visiting ***pda.org/2017PFS*** (Pre-filled Syringe) or ***pda.org/2017Combo*** (Combination Products).

Extend your learning on these important topics when you stay on to take part in PDA Education's *Technical and Regulatory Challenges of Drug Delivery Combination Products – Prefilled Syringes, Autoinjectors and Injection Pens* course on **May 12**. Register today at ***pda.org/2017TRC***.

*Published online first
letter.pda.org

2017 PDA Pharmaceutical Quality Metrics and Quality Culture Conference

Quality Metrics to Impact Pharma Sectors

The recent 2017 PDA Pharmaceutical Quality Metrics and Quality Culture Conference *in Bethesda, Md., offered attendees an opportunity to discuss the current state of quality metrics in light of the recently revised US FDA guidance on metrics. In the second plenary, panelists representing different segments of the industry offered their perspectives on the Agency's quality metrics initiative. Below is a sampling of the panelists' responses.*

Large Pharma

Barbara Allen, PhD, Senior Director, Global Quality Systems, Eli Lilly

Many companies that I'm involved with on the large pharma side have quite a diverse range of products, and one type of product that's coming up quite a bit in conversation is how to address drug/device combination products and how to report them. In general, most are interpreting that if the product is registered with CDRH, that it would not be within the scope of reporting, and that it would be the products registered under CDER that are reported. Then for the metrics, trying to distinguish the drug element and the device element is under consideration, where I would say a lot of the emphasis is on the drug part and the device part comes into play at the very end, but the constituent parts of the device are not being considered as intermediates. I think it would be a complicating factor at this point…in addition, similarly for the API reporting, an emerging common interpretation I'm hearing is all steps of the API, from the first registered starting material to intermediate steps are in scope. This typically extends the supply chain significantly, which increases the number of sites and data points...so we need some clarity on that scope, and perhaps...it may be wise to start with the API step instead of all the individual steps. I think some clarity around that would be very helpful.

Generics

Deborah Autor, Head of Strategic Global Quality and Regulatory Policy, Mylan, representing the Association for Accessible Medicines (formerly Generic Pharmaceutical Association)

I do think it's important to make sure everybody knows that generics are actually 89% of the drugs prescribed in the United States...so, I speak from that perspective, with the understanding it's that scale, that volume, and that low cost model...that, of course, means you have to figure out ways to operate more effectively and be sensitive to cost....

I think the No. 1 challenge for us is that timeline for implementation...I think the Agency has a lot between the first draft and the second draft of the guidance to clarify. There are still a lot of open questions as to how to implement that...I'll say opening it up for a month, for us to submit our data, that's a short window of time, and realigning APR submissions—whatever we do to connect with FDA's annual reporting, which the Agency wants so it can match the datapoints, is going to be challenging. For a proposed solution, I'd say slow down that phased approach. Start with a small number of metrics, a small number of players, and have verification to go along... especially when you have senior management who say "I want to be on the Reporters List." I think my suggestion would be to perhaps scale back the Reporters List. I really do worry about companies taking resources from the quality unit because those are the resources that are doing this, and taking them from something they were doing and changing their tasking toward metrics because that may not be the most impactful thing they could do from a quality standpoint...my point is that it has a huge impact when you look across a large complex company, and I think even the smaller companies, it's going to have a really big impact...do I think this is the right course to pursue? I think from a benefit burden analysis, I'd say at this point, I don't think we're there...If I could know three things about my sites, it wouldn't be lot acceptance rate, invalidated OOS, and product quality complaint rate...I think I'd look at it more like an MHRA approach...things that really get to qualitatively what's happening at a site.

API Supplier

Guy Villax, CEO, Hovione

To answer the question on where is quality metrics going, I have a dream...I wrote about the Dean's List, that the FDA should have a Dean's List, in 2013. And the reason for this is that FDA is amazingly effective at using the stick and getting the wrong people to be out of business or to improve themselves or to stop that product from reaching the pharmacies. And that's wonderful. They do a really good job. The other really good job they do is to push this industry, which takes great risks on new products but is very conservative in manufacturing, and it pushed us with the risk assessment and it pushed us with PAT, it pushed us with QbD. They've done an amazing job to revolutionize the industry. And when they speak, it's much louder than what they think, and they have a far greater reach than what they think but they have not been able to help us in industry by telling us what's good. So at one end of the distribution it's very, very clear what's bad. Crystal clear. Form 483s, Warning letters, etc. At the other end, which is [made up of] the ones that go beyond [just compliance] and do it better and want to improve, FDA has no way of telling us because they have no Form XYZ to say "well done!"...now I think [if] the quality metrics remains voluntary as opposed to compulsory, it means they're going to ignore the majority of the companies doing okay but don't try to do that much better. This is great, let's just ignore them...because what we want is to push those that want to be much, much better, and to be rewarded by being singled out in the Dean's List.

Let me add something, I felt that...the three quality metrics picked—I find them incredibly 20th Century. Incredibly 20th Century. I mean, when we have such amazing, powerful computer [programs], we have huge amounts of data [available] about our [manufacturing]

sites, why do we pick three measures that you're certain everyone's going to game...what I would imagine is the right way is the use of Big Data, so that you can measure risk [holistically and in an unbiased manner]. You can measure the key weaknesses and strengths of the sites. And if you use Big Data, then you can't game them.

OTC

Carol Montandon, Chief Quality Officer, Vice President, Quality and Compliance, Johnson & Johnson Consumer

There are certain consumer products that you would logically think would be well within the FDA's target for metrics, and those are some of the ones that my company sells, such as OTC medicinal products for pain or cough and cold symptoms. But, I also have other OTC drugs within the business that I support that are nonmedicinal, such as acne wash, toothpaste, and mouthwash. Some of FDA's stated goals around metrics are to focus on risk to the patients and to avoid drug shortages from a public health perspective. These nonmedicinal, nondose-limiting OTC products would not provide benefit from this program at all. It's hard to imagine a world in which a shortage in toothpaste from a particular manufacturer would cause a public health issue. Same thing with a mouthwash or deodorant. And these products, just by the nature of them, there are hundreds and hundreds of them. All of us are consumers. All of us stand in front of those shelves in our pharmacy or our supermarket and see the plethora of products that are out there, and they constantly are changing—adding a new flavor or adding a new scent. The number of products we launch on a yearly basis is in the hundreds. If we were required to collect this metric data in a very specific manner for submission to the FDA, it will be quite burdensome.

Biotech

Melissa Seymour, Vice President, Global Quality Control, Biogen

From a challenge perspective, and as an industry working with the Agency, there are a couple of challenges in getting people involved you're going to have—most of the people in this room here probably have an intention of participating. There are hundreds, thousands of companies not sitting in this room. So, how do you get information from those companies? How do you get buy-in from those companies? I think the Reporter's List could be beneficial, but it could also be detrimental. It could force companies to not want to be on the lower tier or to not understand what it means to be put out there and therefore not participate. It could have a reverse effect in that consumers may think that just because a company is on that list that the Agency endorses that

organization [that it means all is well, but that may not be the case]. Certainly taking a paused approach on that list would be smart until we get a more scientific understanding of the data that we're getting—the analytics and what it tells us we're getting about those companies. Later on, I think that could be an incentive. I question starting out with the Reporter's List now.

The other challenge I think is on the benefits side. Historically, industry has worked with the Agency on PAT, QbD, and we've had these grandiose ideas about the benefits we're going to get on the backside. And, in all honesty, I have not seen many [benefits.] I think we actually have to show some mutual benefits to the organizations that are participating. And so, maybe, in reality, a small number of companies participating in a pilot will provide the opportunity for the Agency and industry to work together to be able to show that benefit because that will pull others along. This close collaboration needs continued industry/Agency meetings, talking very closely with industry...it may cause us to get to a more innovative technology-accepting situation where companies will work in collaboration with FDA.

API/CMO

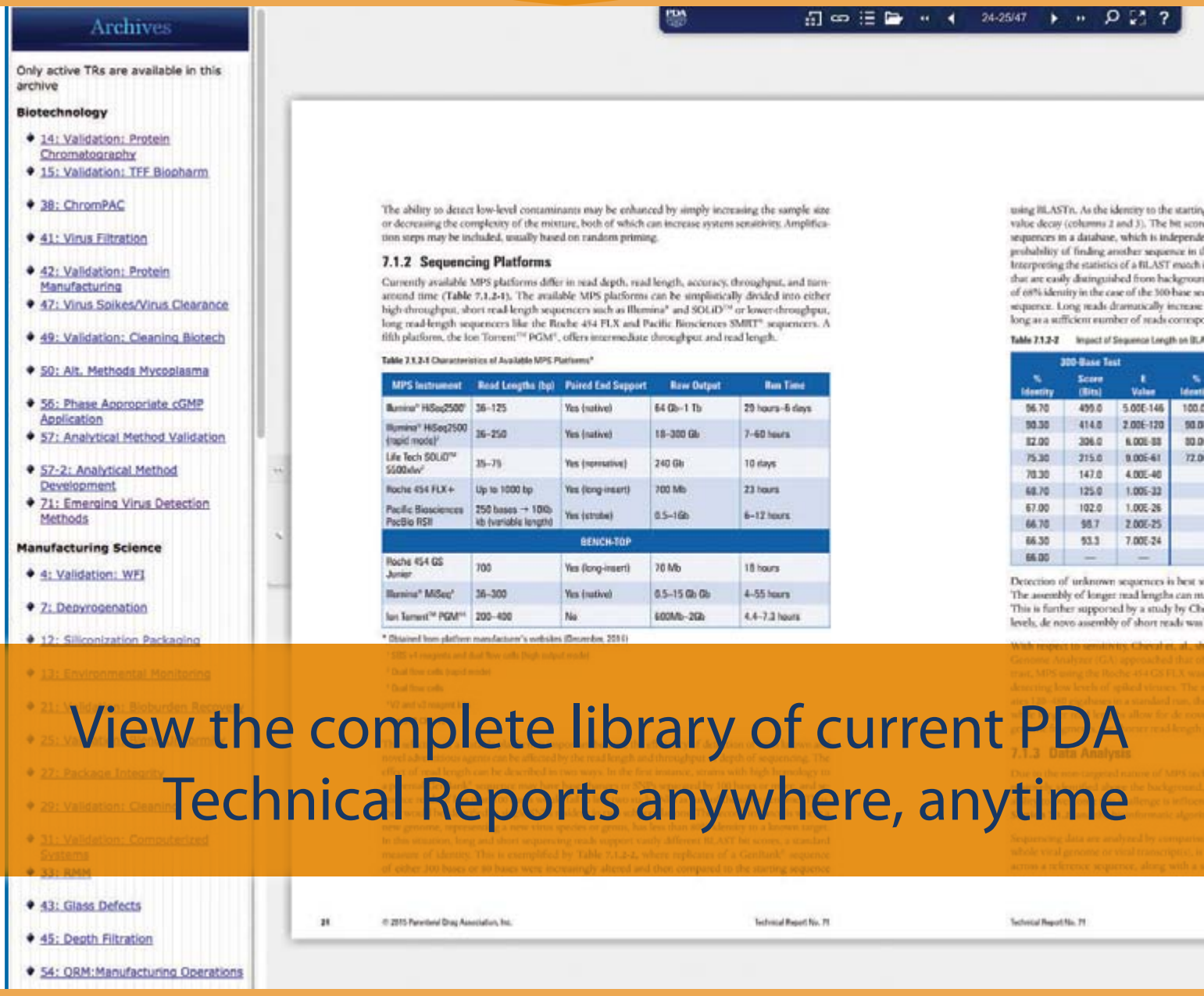
Harry Jeffreys, VP, Regulatory Affairs and Compliance, Catalent Pharma Solutions

In terms of the two challenges that I see, this new site establishment reporting requirement, it's a big one for contractors because certainly we're going to have to report to the license holder about their product and that's pretty significant in and of itself, though we're going to have to report to FDA about the site metrics but understand that that still has to go through the license holder—we have to sit with each license holder and talk about their products and bring it all back together again and put it into a standard format and report it. That's going to be immensely burdensome for contractors. I also think it's going to muddy the waters a bit; there may be some duplication, some confusing metrics that are going to be reported as a result of that. There are a couple of things to support that. A contractor only sees a subset of the data that a product license holder has...your typical test lab may have a purchase order arrangement with a client, and "we're going to use USP test such and such or we're going to do some tests according to a validated method"—but we really don't get the visibility of how that's being used—commercial, clinical development, investigational or some other aspect. That sometimes is clear but often it's not. How should a test site take that and reflect on their quality performance?

I'd like to propose that we create different categories [for site reporting requirements, based upon role, practicalities and potential benefits, up to and including exemption for CDMOs and some other nonproduct license holders from site reporting], similar to what was done for GDUFA II. When it was structured, FDA really took a look at what everybody's role was, and sort of reallocated things. Looking at

Continued at bottom of page 46

PDA's Technical Report Portal



View the complete library of current PDA Technical Reports anywhere, anytime

For more information and to view PDA's Technical Report Portal please visit:

trarchive.pda.org/t/26426

Licensing options available; contact Janny Chua at chua@pda.org

The Parenteral Drug Association presents the...

2017 PDA Biosimilars Conference

June 26-27, 2017 | Bethesda, MD

Hyatt Regency Bethesda

Exhibition: June 26-27

#2017Bio

Register by May 12 and save up to $200

Keys to Developing Effective CMC Strategies for Obtaining Biosimilar Approval

In response to the industry's need for current and reliable information on this rapidly growing area of pharmaceutical manufacturing, PDA is offering the *2017 Biosimilars Conference*.

Benefit from successful case studies and practical examples illustrating how analytical similarity can be demonstrated and practical control strategies can be developed.

Hear current updates from regulatory agencies, including the U.S. FDA, EMA and Health Canada, and CMC reviewer perspectives elucidating those CMC issues that have been most challenging to approve. Attendees will have the opportunity to raise questions and concerns for discussion during the conference.

Attend this important conference to be a part of the interesting and practical discussion on this hot topic.

We look forward to seeing you in Bethesda!

Learn more and register at pda.org/2017bio

IG Meetings to Address Complexity of New Products

Lee Leichter, P/L Biomedical

The unique requirements and challenges related to the development, evaluation, registration, and management of prefilled syringes and combination products have increased in complexity over the last few years and, based on the number of guidance documents from regulatory bodies issued in the last year alone, will only continue to evolve.

For example, in January, the US FDA released its final guidance covering cGMPs for combination products. Weeks later, EMA released its own concept paper on combination products.

To address questions about these regulatory documents and other concerns relating to prefilled syringes and combination products, PDA has organized two back-to-back interest group meetings. The Prefilled Syringe Interest Group will convene May 10, followed by the Combination Products Interest Group on May 11. Experts from industry and the FDA will be on hand both days to outline relevant issues and lead current and prospective interest group members in interactive sessions to clarify requirements and identify potential approaches and solutions.

Current plans are to identify no more than four main topics for discussion within each interest group (two for morning discussions and two for afternoon discussions). There will be a short overview of each topic and, then, experts will facilitate discussions and develop possible approaches or solutions to the topics in question.

Some topics have been tentatively identified; however, in the spirit of interest group collaboration, the interest group leaders would love to hear your thoughts on these, or other topics that would be of interest. Once you register for either meeting, please send your discussion topic suggestions to PDA's **Jason Brown** at brown@pda.org. Any topics not selected for discussion may be used for future interest group meetings.

2017 PDA Prefilled Syringe and Combination Products Interest Group Meetings and PDA Education Course

Bethesda, Md.
May 10–12
www.pda.org/2017pfs | www.pda.org/2017combo

How to Get Your ATMP From the Lab to the Market from page 33

References

1. Livesey, F. "Enabling the emergence of the regenerative medicine industry in the UK." Centre for Economics and Policy, Institute for Manufacturing, University of Cambridge Engineering Department. March 2008. www.ifm.eng.cam.ac.uk/uploads/Research/CIG/Workingpaper3.pdf (accessed Feb. 24, 2017).
2. "Regenerative medicine - Science and Technology Committee Contents," UK Parliamentary Business, 2013. www.publications.parliament.uk/pa/ld201314/ldselect/ldsctech/23/2306.htm (accessed Feb. 24, 2017).

About the Author

Andy Fry is founder of Team Consulting, the Cambridge UK-based medical device design and development organization. He has 30 years' engineering experience in fields including drug delivery devices, surgical implants, and ATMPs.

Updating PDA's Bylaws

Deborah M. Autor, Mylan

Where were you in 1994? No doubt you were not as far along in your career as you are now. You might even have been in school. And, I suppose, some of you may have been too young to even think about your future careers.

In 1994, PDA was reincorporating from the US state of Pennsylvania to Washington, D.C.—and that is also when we last updated our bylaws. A lot has changed since 1994, so we realized it was time to take another look at them. To do this, PDA's Board appointed a diverse committee comprising two current Board members (**Hal Baseman,** who led the effort, and me), a former Board chair and volunteer (**Nikki Mehringer**), a former staff member and volunteer (**Russell Madsen**), the head of PDA's European operations (**Georg Roessling**), PDA's President (**Richard Johnson**), and PDA's legal counsel (**Stephen Schaefer**).

We knew we had to address a few provisions to correspond with some D.C. legal nuances, so we also took the opportunity to simplify the bylaws by clarifying and removing unnecessary language. In addition to modifying what we considered antiquated language, e.g., replacing the word "Chairman" with "Chair," we are taking out references to outdated technologies such as telegrams and faxes. We also allowed for more efficient governance and decision-making while maintaining checks and balances.

There are a couple of significant changes under the proposed new bylaws that I want to point out. First, the Board will now include three appointed Directors and nine elected Directors, instead of 12 elected Directors. The Board will continue to also include the elected Officers of the Association and the Immediate Past Chair. Board members serve a three-year term, meaning that each year, three Directors will be elected, and one will be appointed. The rationale for this is to ensure a diverse representation of all sectors of the industry on the Board. Each year, for the appointed position, the Board's Nominating Committee will recommend a candidate slate, and a Director will be appointed by a majority vote of the Board. The Nominating Committee consists of the Chair, Chair-Elect, and the Immediate Past Chair. For the elected Board members, the candidate slate on which the PDA members vote will have at least two candidates for each open position who have been nominated by the Nominating Committee and approved by the Board. Write-ins are also permitted.

And second, the new bylaws allow for two days' notice of special Board meetings, instead of 14 days. This is consistent with D.C. law and allows the Board to address more quickly major issues of concern. This was not previously possible and the 14-day notice requirement had hindered some Board decision-making. In another modernization move, PDA can now hold electronic Board meetings in certain circumstances.

There are other changes too, but I think these two are the most important. PDA will be speaking to you more about the changes at the Annual Meeting in California and by Web conference and video. We will also post an explanation of the changes on the PDA website. We will then put it to a vote. Please give us your support, and most importantly, please be involved in PDA!

Quality Metrics to Impact Pharma Sectors from page 42

the practicalities, the roles, and potential benefits that participants will see. And I'd say up to and including exemption for CDMOs and other nonproduct license holders from site reporting. [We'd like to see CDMO's exempted from site reporting and have reporting be through the license holder. Quality metrics reporting should be the responsibility of the license holder.]

The Parenteral Drug Association presents the...

2017 PDA Quality Risk Management for Manufacturing Systems Workshop

June 19-20, 2017 | Chicago, IL

Hyatt Centric Chicago Magnificent Mile

Exhibition: June 19-20

#2017QRM

Register by May 5 to save up to $200!

Effective and Practical Application of QRM to the Design, Qualification and Operation of Pharmaceutical Manufacturing Systems

Photo courtesy of Sartorius AG

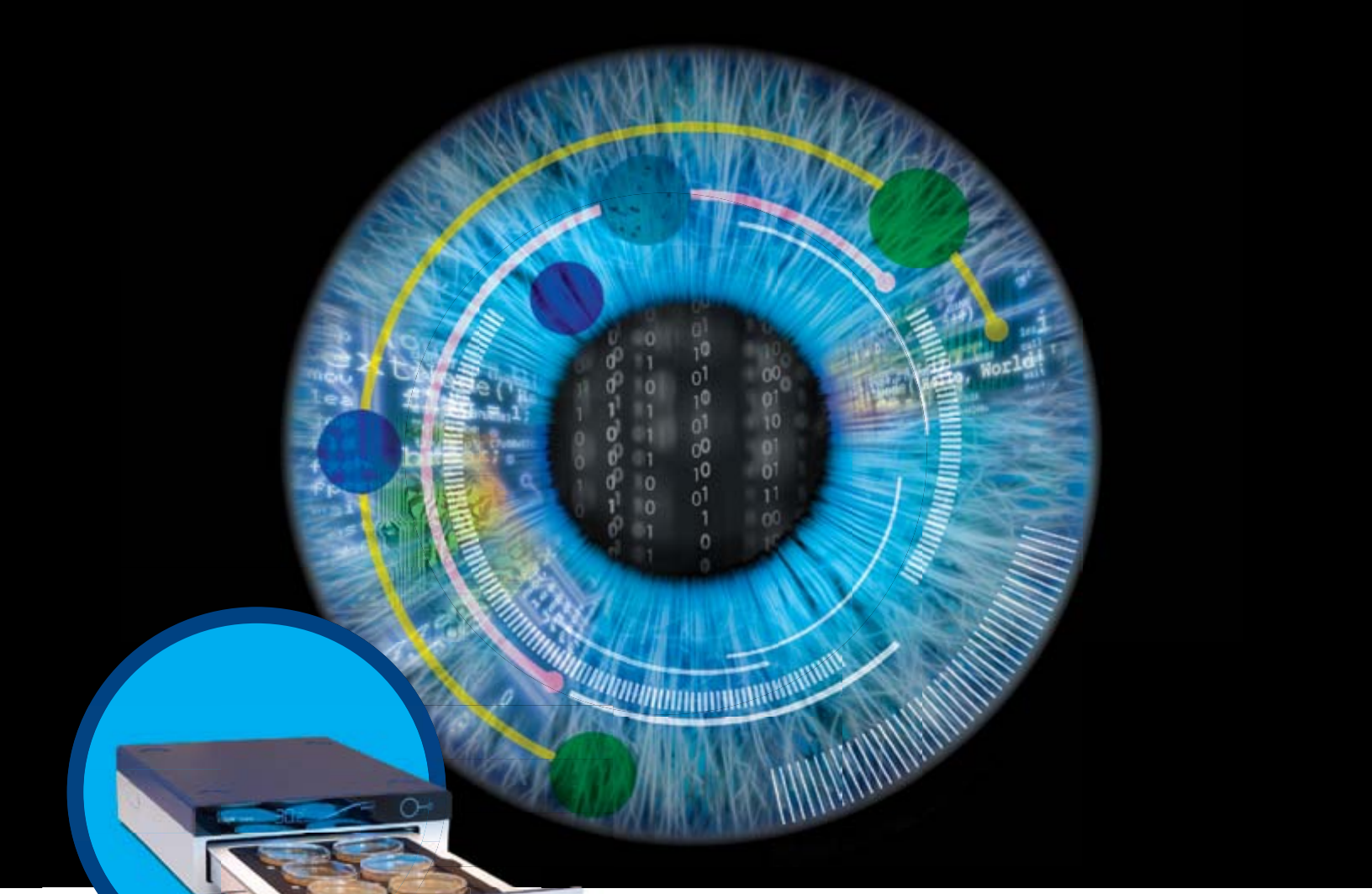
Attend the *2017 PDA Quality Risk Management (QRM) for Manufacturing Systems Workshop*, **Jun. 19-20**, to hear and discuss views, expectations and the newest approaches to science- and risk-based practices for manufacturing lifecycle management. This Workshop will provide attendees with a better understanding of modern approaches for the design, qualification, operation and quality system control of critical process manufacturing systems.

The agenda will include:

- Plenary sessions focusing on the role of QRM, risk-based approaches to system design and practical implementation
- Breakout groups that will conduct a risk-assessment and e strategies for given processes
- A breakfast session meeting of the Quality Risk Management Interest Group
- An evening Networking Reception in the Exhibit Area, where attendees can mingle with colleagues with similar interests and challenges and engage with exhibitors showcasing the latest products and services

Don't miss this opportunity to learn and share best practices on implementation and application of QRM principles.

Learn more and register at pda.org/2017QRM



THERA

EviSight™ Compact

CREATING A CULTURE OF DATA INTEGRITY

INTELLIGENT INCUBATOR AND COLONY COUNTER

BIOMÉRIEUX INDUSTRY

PIONEERING DIAGNOSTICS

www.biomerieux-industry.com