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PDA Letter

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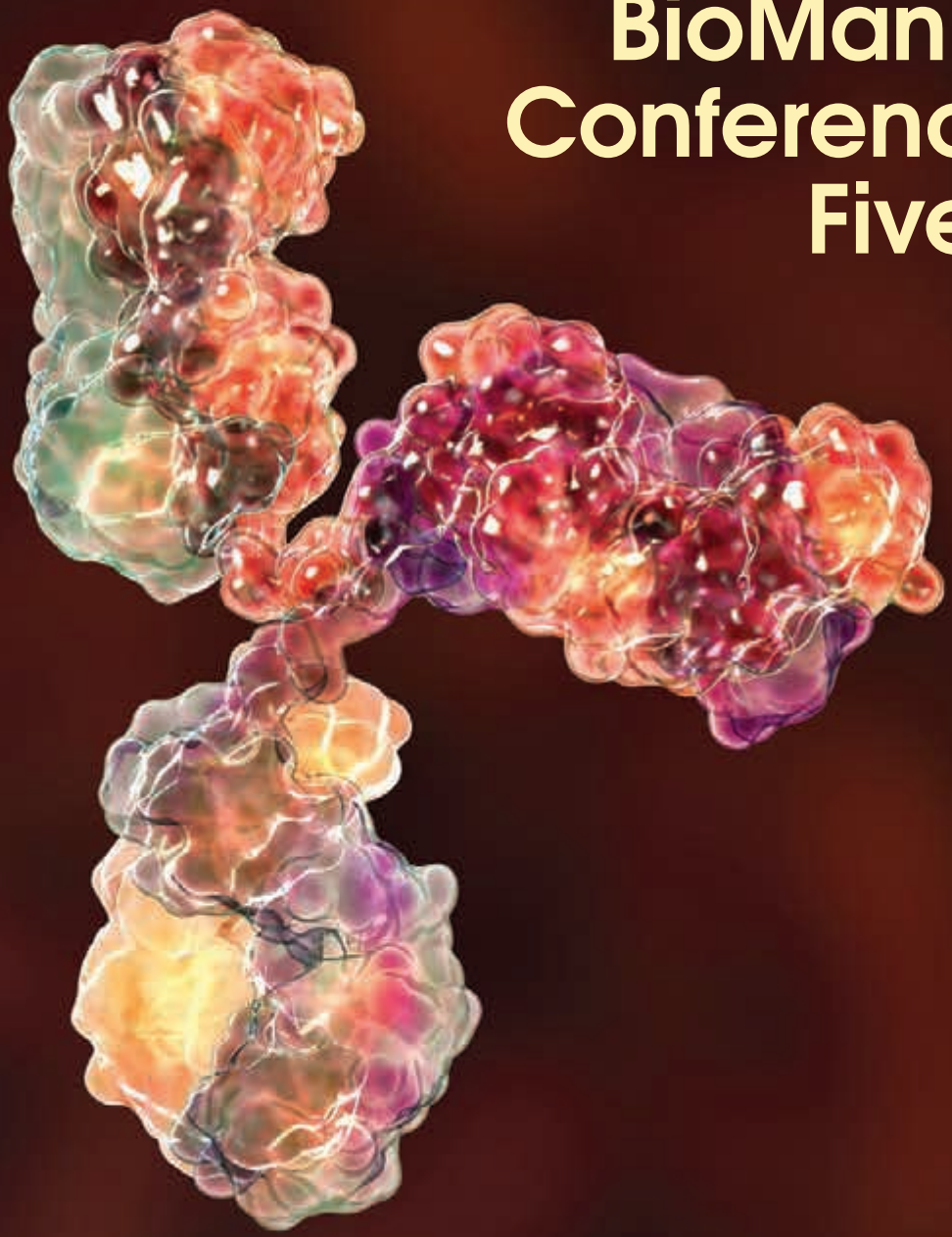

BioManufacturing Conference Tackles Five Issues 16

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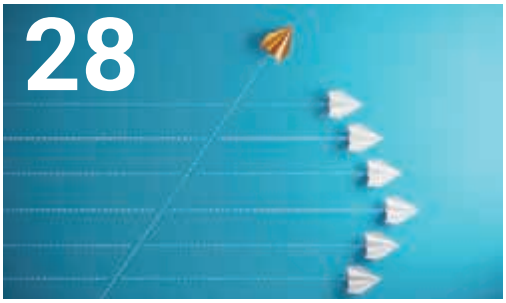

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Articles published in the PDA Letter do not represent the official positions of PDA, Inc., but are the opinions of the authors submitting the articles.

Subscriptions are not available.

Departments

Digital Exclusives

> Special COVID-19 Coverage
Continue to check out the PDA Letter website each week for updated coverage of the COVID-19 situation from PDA members around the world.

> **GMP Tales** | The Case of the B. cepacia Contamination
Learn about a Burkholderia cepacia contamination event and how the U.S. FDA responded in the inaugural episode of the PDA Letter podcast, GMP Tales.

> **On the Issue** | Innovations in Aseptic Processing
Amgen's Chakradhar Padala shares his thoughts on innovative aseptic processing solutions in an On the Issue video.

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PDA Parenteral Drug Association

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GMP Tales

Host Rebecca Stauffer explores the word of sterile drug GMP.

Learn about contamination events, investigations and more!

Episode 1: A U.S. FDA inspector hears some surprising news the Friday before a holiday weeknd.

GMP Tales is looking for future guests.
If interested, contact the Managing Editor at stauffer@pda.org

Available on Spotify, Google Podcasts, Anchor, Breaker, Pocket Casts, RadioPublic and the PDA Letter website.

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More Resources for Pharma

Rebecca Stauffer

@RebeccaStauPDA
www.linkedin.com/in/rebecca-stauffer-782b2310

As I write this, many of our readers within the pharmaceutical and biotechnology industries are diligently working to develop treatments and vaccines for COVID-19 in addition to ensuring stable supply of product in general to patients. I am also happy to see partnerships forming among companies, suppliers and global regulatory agencies which seek to collaborate in a time of crisis.

PDA recognizes that the industry needs as much information available as possible right now. For this reason, all new content on the *PDA Letter* website will temporarily be free for non-PDA members to access. Feel free to forward links to newly posted content on social media and by email to your colleagues.

In addition, we want to hear from our readers worldwide about how the situation is affecting them. Is your company developing a new vaccine? Do you work for a regulatory agency that has suspended inspections? What are your tips for effectively working from home? If you are interested in writing about your experience, please contact me. We plan to post these articles online following an expedited review process.

As another resource, we launched Episode 1 of *GMP Tales,* the *PDA Letter* podcast. Hear Valsource's **Steve Langille** discuss a *Burkholderia cepacia* contamination event he dealt with when he worked for the U.S. FDA. The podcast is available on the Letter website by clicking "Multimedia" on the top navigation. It is also available on Spotify, Google Podcasts, Anchor, Breaker, Pocket Casts and RadioPublic.

PDA staff are also working hard to bring you more information virtually. While our spring conferences and workshops have been either postponed or transformed into virtual formats, PDA also plans to offer webinars featuring subject matter experts. Some PDA Education courses will be offered online. Check the PDA website (www.pda.org) for updates. PDA is also looking for subject matter experts interested in leading webinars and other virtual offerings, so I encourage you to contact PDA.

This is a challenging time for all of us and PDA cares about the health and safety of our members. We will continue to offer expanded online offerings as the COVID-19 situation develops.

Correction

The headshot photos for the co-authors of the article, "5 Challenges of Closed System Transfer Devices," **Cathy Xia Zhao** and **Allison Radwick** were switched on p.48 of the print January/February issue.

PDA Statement Regarding COVID-19

PDA considers safety and health of event attendees as a subject of utmost importance. This is relevant as attendees from various countries, regions, and continents will come to PDA events. The coronavirus outbreak is a global concern. Our sympathies are with those affected around the world.

PDA is committed to maintaining opportunities for volunteers and individuals from the pharmaceutical industry to meet, wherever we can do so. PDA relies on experts in that field, from global bodies like WHO, to national and local health authorities where we are running events, to provide appropriate guidance.

PDA has implemented a set of measures to protect participants and staff from potential risks related to COVID-19 as best as possible. This includes a close and regular monitoring of the situation, adherence to recommendations of health authorities and official travel warnings, possibilities of remote presentations, and precautions being implemented at our venues.

For PDA staff, we are suspending all business travel, until further notice. Our Pandemic Preparedness Plan is in effect, and began teleworking for all US and EU employees on March 16, 2020. We will continue to monitor the situation and make other announcements, as necessary.

PDA EVENTS

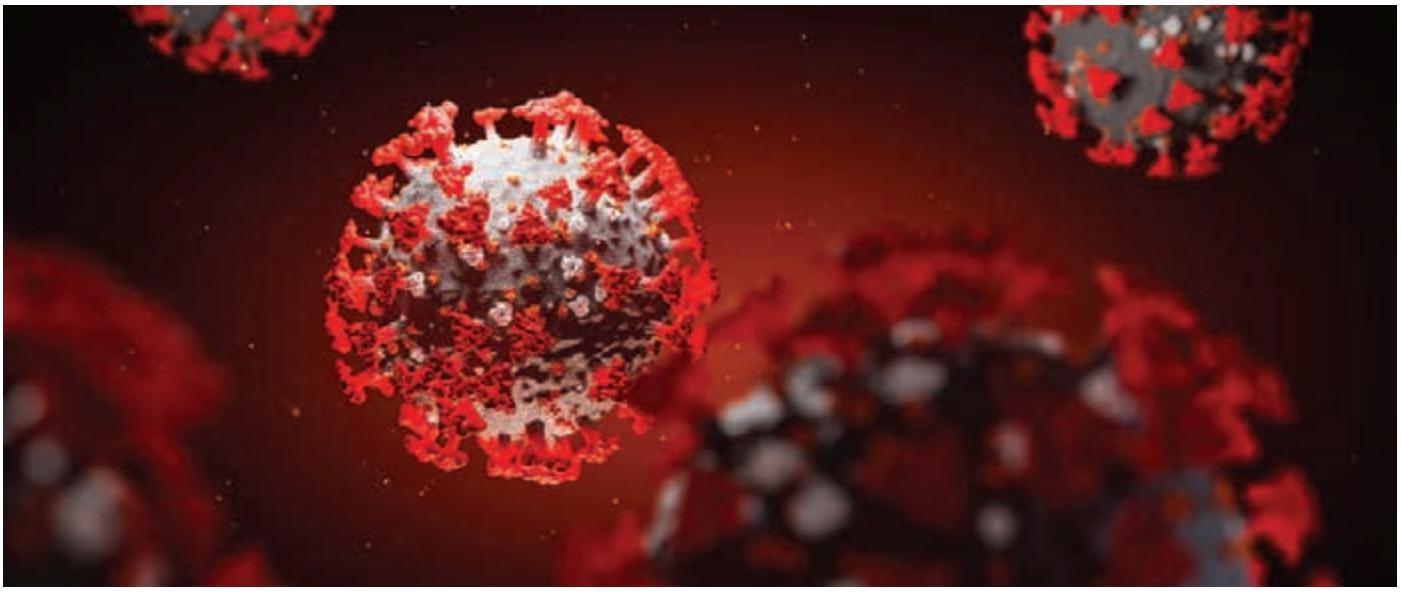
- *2020 PDA Annual Meeting* in Raleigh, NC, was rescheduled to July 20-22, 2020. We are moving to a Virtual Only meeting
- The *Visual Inspection Forum* (EU) planned for April is being moved to October.
- Interphex moved from April to July
- We are repositioning the ATMP Conference in June (US & EU) to Virtual Only.
- We are repositioning the Virus Conference in June (EU) to Virtual Only.
- We are repositioning the Quality & Regulatory Conference in June (EU) to Virtual Only.
- Our staff is urgently evaluating different technical platforms for Virtual events & Exhibitions and we will announce shortly.
- All Training in Europe and US has been cancelled or rescheduled through May.
- We are rapidly assessing conversion of lecture-based training to Virtual.

We have suspended the expiration of existing memberships until the end of June, 2020. As of now, all members will continue to enjoy the benefits of membership even if you are unable to pay due to the impact of the corona virus pandemic.

Be assured that we will continue to operate and provide the service that our members have come to expect from PDA.

PDA will continue to monitor the situation and make additional announcements as the conditions require. If you have any questions, please contact us at info@pda.org.

We caution everyone to be vigilant and refer to the guidance of the worldwide authorities.



PDA Responds to the Novel Coronavirus Situation

Richard Johnson, PDA President

Like me, you have probably been monitoring the developing novel coronavirus situation. We are all worried about the impact to our families and our communities. We are especially concerned about those whose health has been impacted, and all whose daily routines are being disrupted. Every day, we are busy checking the latest updates, so that we can assure we are taking appropriate steps to safeguard the health and safety of our global members and staff.

Our community has a unique challenge; while we are protecting ourselves and our community, many of you have the responsibility to continue to provide critically needed healthcare products. On behalf of PDA, we want to thank you for your efforts!

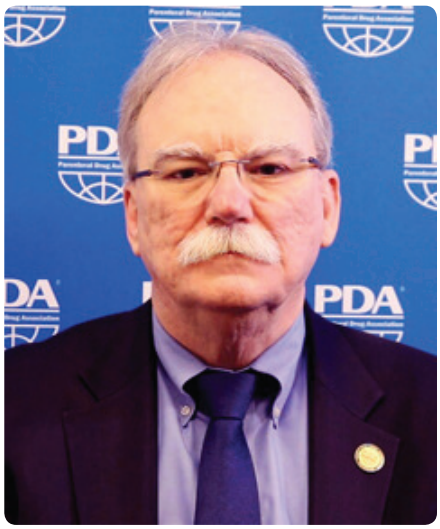
Some of the actions that PDA and our partners are taking include:

- Close and regular monitoring of the situation, adherence to recommendations from global regulatory bodies, and official travel warnings.
- Rescheduling events or changing the format from in-person to virtual events.
- Accelerating the development of online and virtual training for our community.
- Implementing a pandemic preparedness plan for our global staff, including expanding our Work from Home program, and assuring accurate and timely information according to CDC and WHO recommendations.

Regarding upcoming PDA events in the United States and Europe, we will continue to monitor the situation and make additional announcements as the conditions require. If you have any questions, please contact us at info@pda.org.

I also encourage our members to follow updates and announcements from their countries' public health agencies. WHO, EMA and the U.S. CDC, among others, are sources of additional information. See the box below for details.

Please continue to check the PDA website (pda.org), PDA Connector email, *news uPDAte* and *PDA Letter* for further information about the impact of COVID-19 on PDA activities.



Additional Resource Links:

World Health Organization (WHO) — Novel coronavirus (2019-nCoV) outbreak
https://www.who.int/emergencies/diseases/novel-coronavirus-2019

U.S. Center for Disease Control and Prevention (CDC) — 2019 Novel Coronavirus
https://www.cdc.gov/coronavirus/2019-ncov/index.html

European Medicines Agency (EMA) — Novel coronavirus
https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19

Government of Canada COVID 19 Update
https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection.html

European Center for Disease Prevention and Control
https://www.ecdc.europa.eu/en

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PDA Welcomes Glenn Wright

PDA is pleased to announce the appointment of former Eli Lilly and Co. executive **Glenn E. Wright** as Vice President of Scientific and Regulatory Affairs. He joined the Association March 23.

As PDA's Vice President of Scientific and Regulatory Affairs, Wright will oversee PDA's scientific and regulatory affairs activities, which include developing industry-leading technical reports, the standards program through the American National Standards Institute (ANSI), regulatory commenting, and collaborating with PDA's technical/regulatory advisory boards.

Wright's career at Eli Lilly spanned more than 20 years, during which he served in a variety of functions that give him unique experience in both pharmaceutical science and regulatory affairs. These roles included auditor, QC manager, global regulatory affairs director, and senior director of manufacturing science and technology.

"Mr. Wright's long experience in sterile pharmaceutical manufacturing, control, and regulatory affairs will prove invaluable to PDA's members," said **Richard Johnson,** President and CEO, PDA. "I have known Glenn a long time both during my time as PDA President and as a volunteer before that, and I am confident Mr. Wright will be an excellent leader of PDA's various regulatory and manufacturing science activities."

Wright has also been active with PDA since 1990. He served over 12 years on the PDA Board of Directors, over 10 years on the PDA Science Advisory Board, and most recently as co-chair of the PDA's Aging Facilities Task Force and as co-chair of PDA's Manufacturing Science and Operations Program.

He replaces **Tina Morris,** PhD, who joined PDA in 2018 and oversaw the development of PDA's first six standards. She left PDA to become the American

Association of Pharmaceutical Science's executive director.

"PDA appreciates Dr. Morris's leadership during a time when PDA was drafting its first standards," said Johnson. "We know AAPS will be in capable hands, and we wish her good fortune in her new role."

Annex 1 to VPHP: The ABCs of Aseptic Processing

Shelly Henderson

Technological changes are coming to aseptic processing, as acknowledged by regulators and reflected in the recent draft Annex 1 revision. What are some of the latest trends in this area? How can pharma prepare?

Three speakers offered their thoughts on the latest developments in aseptic processing at the PDA New England Chapter dinner meeting, held in Lenox, Mass. on Nov 3. Former PDA Chair **Hal Baseman** explained how the proposed draft Annex 1 revision will impact aseptic processing technology. **Samantha Kay** looked at validation of vapor phase hydrogen peroxide (VPHP or VHP) decontamination. **Shawn Kinney** concluded the talks with a look at the latest in isolator technology.

Annex 1 represents the first new discussion on aseptic processing in a while, Baseman explained in his presentation. The document contains 43 recommendations for risk-based approaches to sterile product manufacturing and control and sets an expectation for the use of quality risk management (QRM) principles. Why is this important? Well, if regulators expect industry to use QRM to justify submissions, then it would follow that QRM could be used to justify new regulations.

The second part of Baseman's presentation focused on current industry trends. He exclaimed that the rate of change is not fast enough! We are entering an unprecedented era with new therapies; competing demands of affordability, sustainability and public safety; improved manufacturing reliability; and new technology resources such as artificial intelligence and big data.

Baseman outlined key trends affecting our industry:
1) Transition from manufacturing processes that are batch-driven, single-shift, intervention-laden, personnel-dependent and environment-constrained to those that are continuous, automated, small-closed-environment, data-driven, data-controlled and standardized.

2) Transition from approaches to control that are corrective and reactive to those that are risk-based and preventative.

3) Transition to more objective sterility assurance based on data.

4) Transition to greater transparency and exchange of ideas across the industry.

5) Transition to increased cooperation among manufacturers, suppliers and regulators.

Following Baseman's presentation, Kay covered VPHP decontamination—a decontamination method growing in popularity. VPHP is a surface biocide requiring contact for successful decontamination. Lack of contact results in inefficient decontamination, a major concern within the industry. Since spore dispersion can be affected by material topography (roughness, grooves, or cavities), one method to predict material compatibility is to inoculate material with 10^6 *Geobacillus stearothermophilus* spores and then analyze with a scanning electron microscope.

The following concerns, however, should be heeded with VPHP:
- Some substrates show poor spore dispersion and should be avoided
- Hydrogen peroxide (H_2O_2) contact may produce deterioration of elasticity, strength or flexibility of different materials
- H_2O_2 may be absorbed by the package material or contents.

Kay presented a series of case studies to show how these challenges may be overcome.

Rounding out the discussions, Kinney's presentation debunked five myths regarding isolator technology. First, isolator systems are *not* more expensive than cleanrooms. Since only a grade D background is required for operator areas, there is no need for sterile gowning. This lowers the cost of quality greatly due to reduced excursions, deviations, and monitoring of personnel and the environment. Second, VHP's effect on product is miniscule as no primary containers are exposed to VHP and thorough aeration to 1 ppm VHP or lower is achieved before product exposure. Third, cycle times are *not* longer. Current cycle times are one to four hours with greater than 6-log reduction of microbes, which is essentially sterile. Fourth, validation is *not* more difficult. Kinney's company has successfully validated isolators from three different manufacturers, demonstrating that 650-760 ppm for approximately 30 minutes achieves 6-log reduction of *Geobacillus* spores.

Fifth and finally, Kinney showed how isolator systems can be flexible. His company has implemented two filling lines: a manual line that uses an isolator and a dual-chamber, restricted-access barrier system (RABS) for filling vials, syringes and cartridges up to 5,000 units each and a semi-automated line which integrates four isolators, three RABS, a depyrogenation oven, a capper and a lyophilizer. Kinney demonstrated that flexibility can be designed into an isolator by manufacturers who cooperate to fabricate and integrate their equipment into the isolator.

All in all, it was a successful event. Before the talks even began, the 58 attendees had the option of touring Berkshire Sterile Manufacturing's facility. The event concluded with a surprise birthday cake for Kinney, in honor of his special day.

The chapter thanks the three speakers and meeting host **Henry Brush** along with all the sponsors for making this event possible.

PDA Who's Who

Hal Baseman, COO, ValSource

Henry Brush, Vice President, CMC Strategy and Operations, Selecta Biosciences, and Chapter Member-at-Large

Samantha Kay, Microbiologist, Fedegari Technologies

Shawn Kinney, PhD, CEO, Berkshire Sterile Manufacturing

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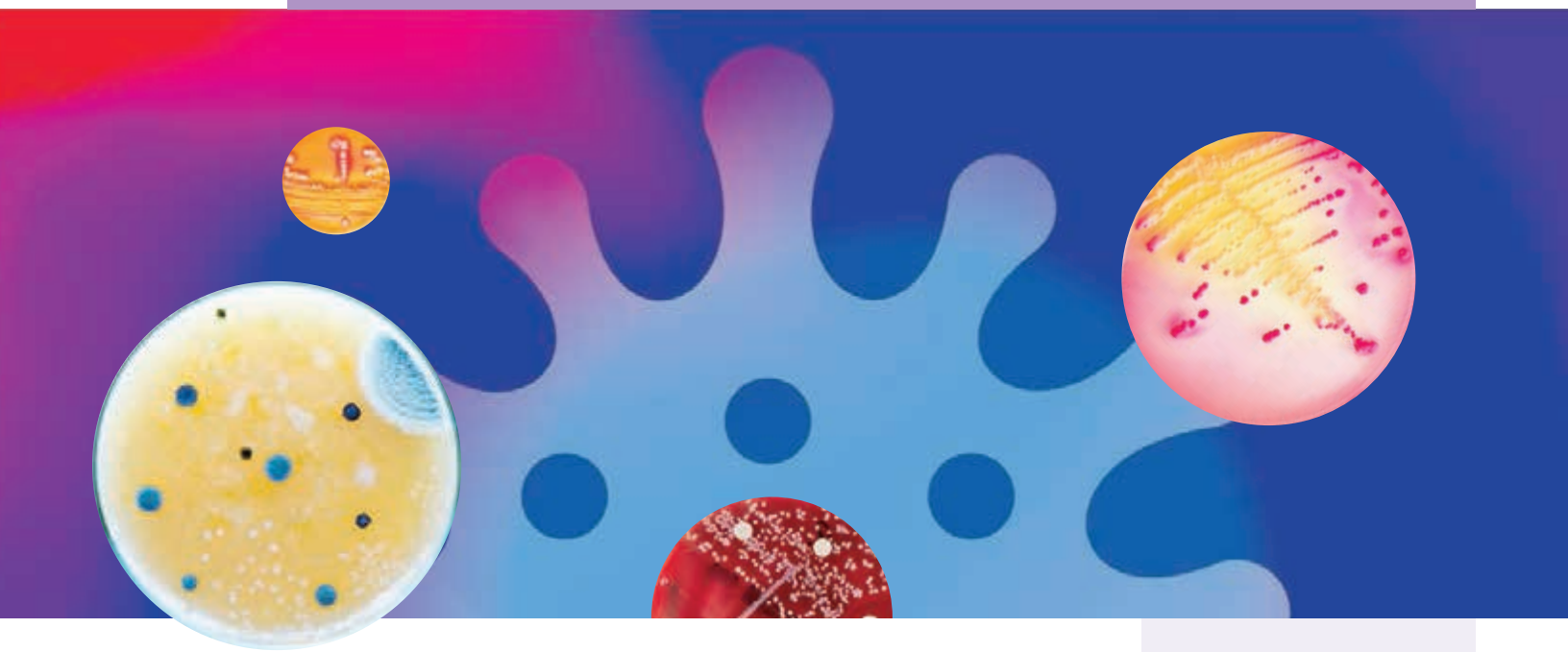

Fifteen years after the inaugural *PDA Global Conference on Pharmaceutical Microbiology*, we are continuing to explore the most relevant topics in pharmaceutical microbiology.

In this milestone year, the agenda will stay true to tradition and move the conversation forward with in-depth panel discussions, breaking down barriers and sharing the perspectives of both industry and regulatory representatives.

To learn more and register, visit *pda.org/2020micro*

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EXHIBITION: OCT. 19-20
2020 PDA RAPID MICROBIOLOGICAL METHODS WORKSHOP: OCT. 21-22
TRAINING COURSES: OCT. 22
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Tools to Address Human Error Reduction

PDA Pacific Northwest Chapter

No human is perfect. That is a given. So how can we help prevent issues due to human error during the pharma manufacturing process?

Virginia Andreotti-Jones provided some tools for members of the Pacific Northwest Chapter in the introductory seminar, "Human Error Reduction," held Oct. 24, 2019, in Seattle.

Andreotti-Jones began with a look at the foundations of human error reduction. The first step, she said, is accepting that all people make mistakes. This means assuming no malice on the part of the individuals involved, avoiding blaming language, keeping communications open and focusing on a system approach to resolving the issue.

Next, she outlined two tools for preventing human errors. The first, a pre-job briefing, is given prior to an activity with a discussion led by front-line personnel. This meeting should take about 10 to 15 minutes to discuss the task, documentation, roles and responsibilities, critical steps, potential errors and mitigation, operator tips, troubleshooting strategies and stop-work points.

The second tool, according to Andreotti-Jones, is a root-cause decision tree. The decision tree takes a systematic approach to assess materials, machinery, maintenance, measurements, the environment, methods and training. It helps ensure systems are analyzed to identify and eliminate underlying causes of human error. This approach leads to more meaningful CAPAs and prevents human error in the future.

Examples of both tools and case studies of their use can be found on the Pacific Northwest Chapter website: https://www.pda.org/chapters/north-america/pacific-northwest.

PDA Who's Who

Virginia Andreotti-Jones, QA Supervisor, Partner Therapeutics

PDA Parenteral Packaging 2020
February 25–26 | Basel, Switzerland

(l-r) Herve Soukiassian, BD; Folker Steden, SCHOTT; Joerg Zuercher, Bayer; Roman Mathaes, PhD, LONZA; Galen Shi, PhD, Eli Lilly; Bettine Boltres, PhD, West; Falk Klar, PhD, President, PDA Europe; Derek Duncan, PhD, Lighthouse Instruments; Roger Asselta, Genesis Packaging Technologies; Robert Guidos, Corning; Yusuf Oni, PhD, Bristol-Myers Squibb; Renaud Janssen, Phd, Datwyler

Co-chairs Galen Shi (left) and Roman Mathaes (right) prepare to cut a cake in recognition of the tenth anniversary of the Parenteral Packaging conference

BioManufacturing Conference Tackles Five Issues: Part I

Michael DeFelippis, PhD, Eli Lilly, and Cristiana Campa, PhD, GSK

Monoclonal antibodies. Vaccines. Advanced therapy medicinal products. All of these biologics face common manufacturing challenges.

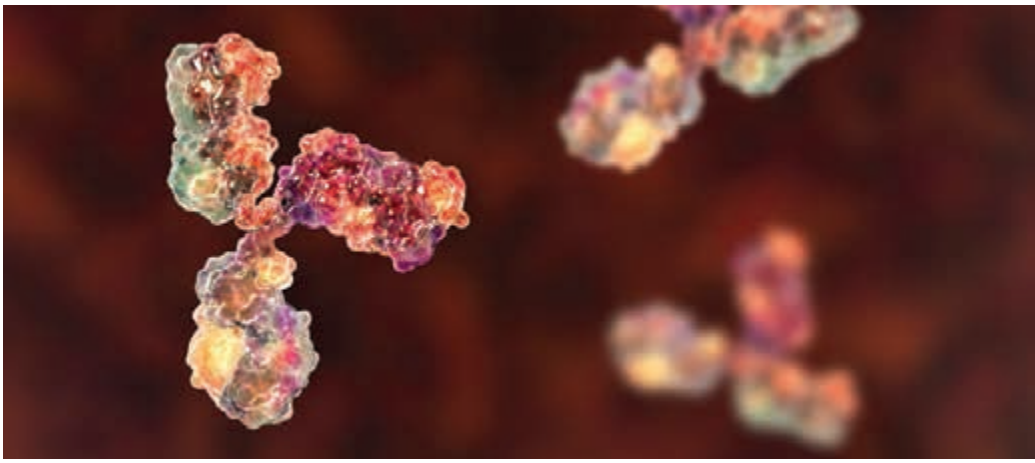
In recognition of this, PDA initiated a new conference devoted solely to the science and technology of biopharmaceutical production. The inaugural *BioManufacturing* meeting took place Sept. 3–4 in Munich with a primary objective of creating a forum for discussing current trends and novel approaches affecting a variety of biopharmaceutical product classes. There are common manufacturing practices, issues and challenges related to monoclonal antibodies, vaccines, and other therapeutic proteins; therefore, the broad scope of the conference emphasized importance of connecting these different product platforms and created opportunities for shared learning across different disciplines.

Topics included accelerated product development, raw material quality, facilities, upstream/downstream process development, quality-by-design, quality risk management (QRM), single-use systems, continuous manufacturing, modeling and simulation, automation, analytical testing, control strategy, microbiological/viral control, aseptic processing, drug product formulation and delivery, combination products, supply chain, knowledge and lifecycle management.

While there were many points of discussion, five in particular—outlined in **Figure 1**—emerged as overarching themes driving the future of biomanufacturing. These themes are discussed in greater detail below.

Theme 1: New Technologies and Novel Modalities

Both industry and regulators seek to use advanced CMC solutions to accelerate access to medicines without compromising quality. The opening plenary summarized key points taken from the from the EMA/FDA 2018 workshop on quality support to priority medicines and breakthrough therapies, which covered eligibility, quality challenge and regulatory aspects for priority medicines (EU) and breakthrough therapies (U.S.) ***(1).***



In this session, regulators **Dolores Hernan**, PhD, Quality Specialist, EMA, and **Mats Welin,** Senior Expert, Swedish Medical Products Agency, reviewed details of the EU Priority Medicines (PRIME) scheme discussing eligibility, quality challenges, regulatory aspects and they supported the information with case studies ***(1).*** The PRIME program is intended to support the development of medicines with major public health interest. Very few applications are accepted and as of July 14, 2019, only 11 of 45 were granted. Hernan grouped challenges into three categories: 1) timeline; 2) innovation and complexity and 3) global development, while pointing out that the content of Module 3 must be in line with scientific guidelines and technical requirements defined in EU legislation. Welin's overview of the joint EMA/FDA workshop highlighted how regulators are working collaboratively to support sponsors in managing these challenges. Discussion topics from the joint workshop included: identifying scientific elements/tools within existing guidance, identifying gaps in current guidance and exploring areas of common agreement and further harmonization between EMA and FDA.

Further considerations from Industry were discussed in a dedicated breakout session on "Accelerated Access." **Mic McGoldrick,** Associate Director, Global CMC Policy, MSD, shared his presentation, "Challenges for Registration and Opportunities to Increase Alignment of Requirements in Emerging Countries," which emphasized that registration harmonization is key to expediting vaccine availability and it ultimately benefits lifecycle managements. He pointed to several areas (e.g., common application forms, reliance on inspection through PIC/S, nonduplication of testing, and rational requirements for local/regional clinical tests) where harmonization seems feasible.

A presentation from **Amin Khan,** Vice President and Head, R&D Acceleration Team, GSK Vaccines, offered some thoughts in his talk, "CMC Criteria for Accelerated Access of Vaccines," focusing on relevance of QbD-driven risk-based approaches. He provocatively stated that "moving away from 'process-is-product' (of new vaccine development)" is critical. Khan emphasized possibilities for early product understanding and tailored analytical and comparability

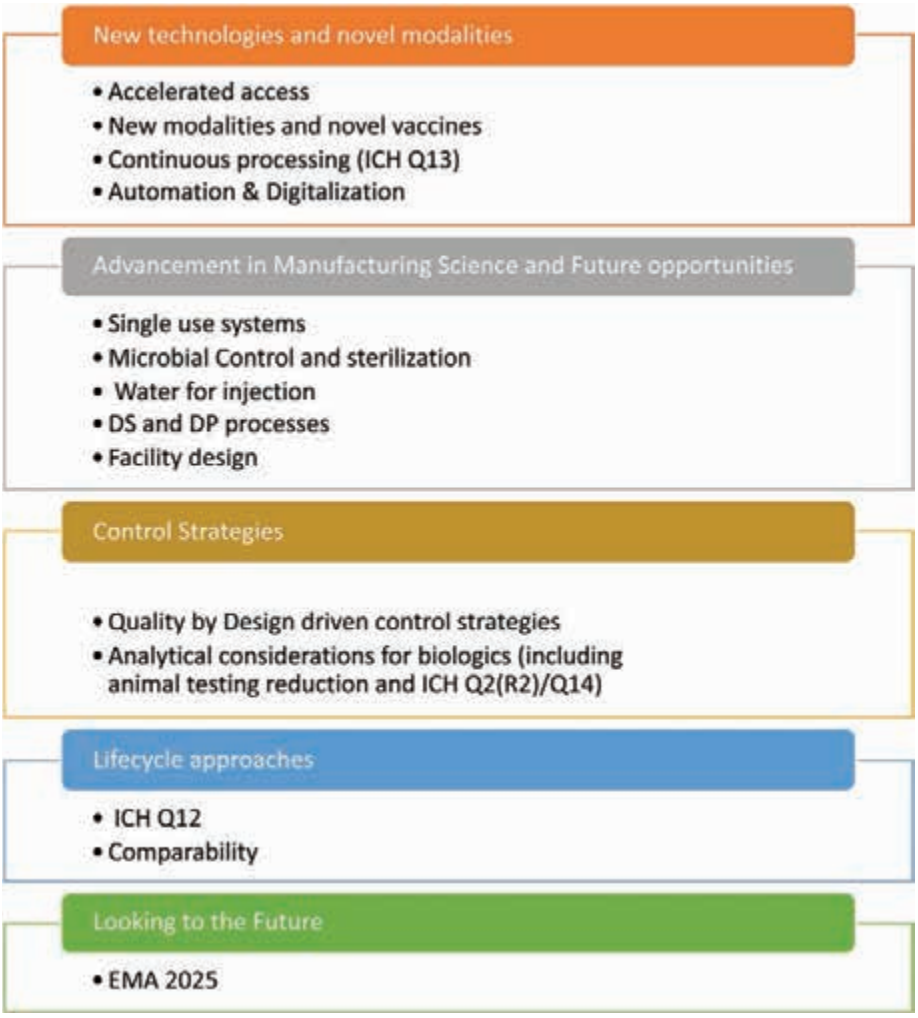


Figure 1 Top 5 Overarching Themes Driving Future of Biomanufacturing

strategies in the vaccine arena, allowing deferral of selected CMC activities without compromising product quality and ultimately safety and efficacy.

A session dedicated to "New Modalities and Novel Vaccines," brought focus to the manufacturing challenges for newer product types for which industry experience is limited. New products like advanced therapy medicinal products (ATMPs) or novel vaccines will not only require more complex strategies but also flexible concepts for manufacturing. Consequently, risk-based approaches for process design and control strategy are essential, particularly since these products often involve accelerated approval pathways. Using synergies between vaccines and therapeutic protein products, development and manufacturing could trigger faster solutions for new disruptive technologies.

Building on the opening plenary session, **Wilhelm Herok**, Manager, Austrian Agency for Health and Food Safety, provided a regulatory perspective on the challenges of developing ATMPs within accelerated timelines. Herok stressed that the compressed CMC timelines for ATMPs will likely result in limitations in manufacturing experience, product characterization and stability data, and analytical development. His advice to overcoming these challenges included implementing broad assay development early in the product lifecycle, aligning analytical and process development, avoiding major changes in analytical methods, early product characterization, collecting as much supporting stability data as possible, implementing changes early in development and avoiding major changes during pivotal clinical trial(s), retaining sufficient samples for comparability studies, and effectively using risk assessments to justify strategies.

Industry reflections on manufacture of new modalities were shared by **Uwe Gottschalk**, Manager, Lonza. In responding to a question on what can be done to address manufacturing challenges associated with viral vector technologies like adeno-associated viruses, Gottschalk emphasized the need for more dialog between individuals working in different disciplines. He believes the viral vector field can benefit greatly from the knowledge accumulated over the years on vaccine production, but to harvest this learning, he pointed out that people simply need to talk to each other. **Michael Hust**, PhD, Group Leader, Technical University Braunschweig, showed a case study, "Fighting Pathogens and Toxins with Human and Human-like Recombinant Antibodies." This case study highlighted how an academic laboratory is currently identifying novel products to address unmet medical needs and seeking partnerships to enable access for patients.

Alvaro Carpintero, Partner, McKinsey & Company, then delivered a keynote presentation on current biopharma trends, leveraging McKinsey's extensive experience on the opportunities that biomanufacturers should embrace to be ahead in the healthcare market. Carpintero focused on digitalization and analytics, given the relevance of the topic to enable acceleration and reliable control strategies. The topic was further discussed during a dedicated session on automation and digitalization. **Sandrine Dessoy,** Senior Manager, GSK Vaccines, showed a presentation on one of the first-ever digital twins for vaccine production. This "real-time digital replica of a physical device" may revolutionize the way control strategy is defined for pharmaceutical products, integrating artificial intelligence, computational fluid dynamics, and process analytics technology (PAT). **Toni Manzano,** Chief Scientific Officer and Cofounder, Bigfinite, showed how artificial intelligence (AI) represents the foundation for the augmented control of the biomanufacturing processes, including some relevant updates on regulatory acceptance of AI. Finally, **Per Vase,** Managing Partner,

NNE, shared a very interesting presentation on big data, clarifying drivers and opportunities, with a focus on the biomanufacturing space, process controls, real-time release and predictive maintenance.

Continuous process control is a prerequisite for continuous processing, which is becoming popular due to the smaller footprint, shorter processing times and increased flexibility. For these reasons, the conference dedicated a session to continuous processing and the new ICH Q13: *Continuous Manufacturing of Drug Substances and Drug Products* guideline. **Ganapathy Mohan,** Executive Director, MSD, a member of the ICH Expert Working Group behind ICH Q13, provided a status update on the guideline's progress. Mohan indicated that alignment has been reached on several key topics so that the drafting process can start. **Klaus Kaiser**, PhD, Head, Downstream, Bayer, shared an example of Continuous Downstream Processing: Comparability and Regulatory Risks. He emphasized that a clear understanding of the process is necessary because the main challenge resides in demonstrating the consistency of the product over time. When switching from a batch to a continuous manufacturing process, the bridging strategy should ideally be discussed well in advance with global regulators. ICH Q13 is still at a very early stage, but there have been many discussions centered on batch size definition for example. What is already clear, is that the batch size must of course be defined before the start of the batch and that the batch size can be defined either by running time or by quantity of material (input or output).

Sebastian Teitz, Product Manager and Scientific Coordinator, Asahi Kasei, then elaborated on the implementation of virus filters in continuous processing schemes. He outlined that virus filtration is already a flow-through process and thus seems very amenable to continuous processing. Also, as a matter of fact, virus filters are able to perform well under a wide range of process conditions. The implications, however, of highly dynamic situations, i.e., if the feed stream varies in conductivity, protein concentration, etc., is only beginning to be understood. The presentation focused on results obtained within a collaborative project with the FDA that addressed this and also validation challenges as well as possible solutions.

Theme 2: Advancement in Manufacturing Science and Future Opportunities

Single-use systems have increased the efficiency of biopharmaceuti cal manufacturing operations by streamlining many unit operations where cleaning of multiuse equipment would be typically required. Single-use systems, however, create challenges with particulate matter control and validation. **Klaus Wormuth,** PhD, Lead Scientist Particles, Sartorius Stedim's presentation, "Reduction of Risks from Particulate Matter in Single-Use Systems" provided a holistic approach and validated methodology for particle matter monitoring and continuous improvement. As industry gains more experience with single-use systems, the technology is being incorporated into manufacturing processes for different classes of biopharmaceutical products, enabling a control strategy on visible particle matter presence. **Josselyn Haas,** Manager, Biomanufacturing Engineering, Merck KGaA, provided a good example of the increased adoption of single-use systems in her subsequent presentation, "Development of a Scalable Adenovirus-Based Rabies Vaccine Based on Single Use Technologies."

The breakout sessions dedicated to "Practical Approaches to Contamination Control" and "Approaches to Microbial Control and Sterilization Methods," focused on the modernization of microbiology. Establishing strategic partnership with innovative suppliers to bring new technology, faster results and less human involvement in the microbial contamination control program is a reality demonstrated by the microbiology modernization cross-industry consortium. Regulators in these sessions express that they are keen to see manufacturing innovation being adopted, but faster acceptance also requires regulatory involvement from the beginning. Such reflections were stimulated by several talks. **Cornelia Haas,** Manufacturing Science and Technology Engineer, VTU Engineering, discussed on contamination control strategies and how they can be developed based on an understanding of the processes, assessment of the risk of failure (or contamination) and the control to be put in place to demonstrate effectiveness of the remediations and procedures in place. **Kavita Ramalingam Iyer,** PhD, Associate Director, Vaccines CMC-Global Regulatory Affairs and Clinical Safety, GSK, presented, "Optimizing Gowning Controls for Reduced Bioburden Manufacturing," describing a revised structured and risk-based approach to defining an appropriate level of gowning for reduced bioburden processes encountered in biopharmaceutical manufacturing without compromising product quality or risk of product contamination. Specifically, she detailed case studies to describe how the assessment can be done for different facility scenarios in order to determine the appropriate gowning levels. This thought supports the innovative concept of flexible facilities or in other words facilities of the future founded on ballroom principles and enables enhanced speed of quality medicines to the market.

Carolin Duignan, Analytical Scientist, GSK, discussed "Advancing QC Microbiology Modernization Through Cross-industry Collaboration." This collaboration is designed to initiate transformational change in microbiology testing by establishing strategic partnerships to enable identification and industrialization of standardized technology platforms and ways of working. She shared a case study and the results of a collaboration between pharmaceutical manufacturers and Biomerieux to develop an automatic system capable of reading microbial counts. **Juha Mattila,** Director, Sterilization Technologies, STERIS, shared a case study on critical process control and monitoring, as well as validation requirements and methods for a VH2O2 low temperature terminal sterilization process. He also presented a case study on a recently FDA-approved product application for using VH2O2 terminal surface sterilization. Finally, **Annick Gillet,** Technical Director EO Pharma, Sterigenics, covered "How to make the Optimal Choice for the Final Sterilization of Pharmaceutical Products" in regard with the recent publication EMA guideline, "'Guideline on the sterilization of

Continued on page 55

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Qualification of Manual Visual Inspection Still Critical

Alexis Flaquiere and Jean Malthête, GSK Vaccines

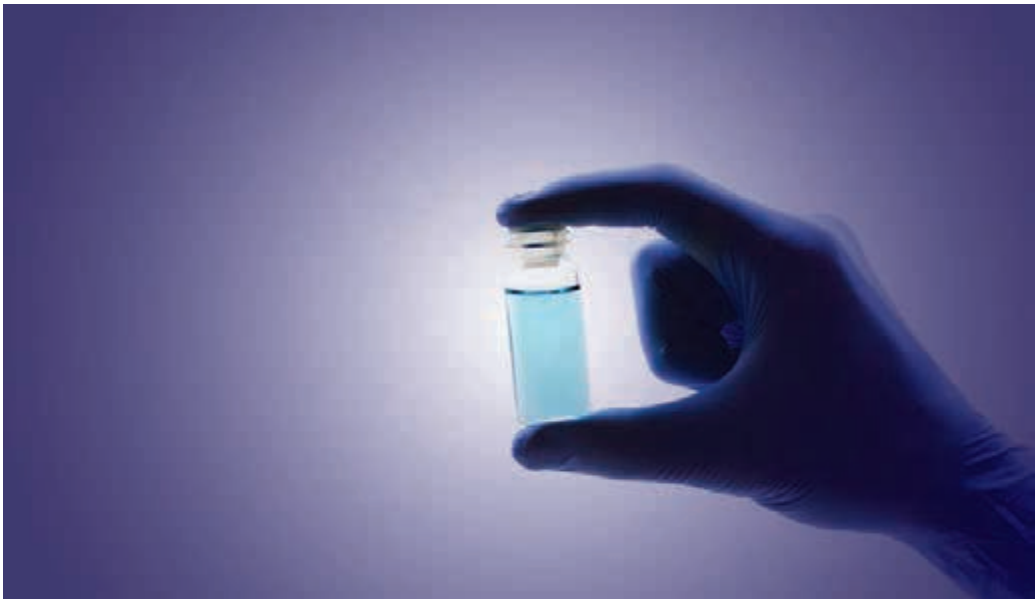
Manual visual inspection is the most common method for performing 100% visual inspection of parenteral liquids and remains a critical procedure that all manufacturers must continue to perform.

Automated visual inspection, with its higher throughput and lower running costs, provides an effective alternative. Automated visual inspection has improved significantly over the last decade with digitalization and data processing, offering manufacturers a consistent process not subject to fatigue or mood.

While manual visual inspection may appear old-fashioned compared to its automated alternative, two constraints demand that manufacturers develop and maintain a high level of expertise in manual visual inspection, even if the volume of manually inspected batches is marginal.

First, according to USP <1790> Visual Inspection of Injections, any alternative to manual visual inspection must be demonstrated to have "equivalent or better performance when compared to manual visual inspection" ***(1).*** The Knapp and Kushner framework provides a recognized methodology to ensure this equivalency; this approach compares the probabilities of detection of defects found by manual visual inspection to the performance of detection by the alternative ***(2).*** An organization with an effective manual visual inspection process has a more robust baseline which, in turn, drives automated visual inspection qualification to the necessary level of performance. Ultimately, this means that automated visual inspection qualification is not based on absolute criteria, but relative criteria.

Second, after 100% visual inspection, a sampling of accepted units of each batch is inspected. This ensures that the remaining level of defects is statistically acceptable. Current compendia and regulations require this inspection to be done manually.



Manual visual inspection brackets visual inspection from the beginning (qualification) to the end (acceptance quality limit, or AQL) of the process, regardless of the complexity and sophistication of automated visual inspection.

As a critical procedure, how can adequate manual visual inspection performance be assured?

A human-based process, the qualification of inspectors is a pillar for its success. Typically, inspectors are qualified using a set of defects among conforming units; the inspector must properly detect defects to receive an "Inspection license."

But what does "proper detection" mean? And what criteria apply?

Is 100% Detection Truly Beneficial?

USP <1790> recommendations are based on the Knapp & Kushner methodology. The first step is calculating the criteria for success for an inspector's qualification. To do this, a group of reference inspectors perform repeated manual inspections. As outlined in Section 7.4, their results are then statistically combined to determine the probability of detection baseline, which is the success criteria for future inspectors.

Then, distinct criteria should be defined for each defect class (i.e., criticality).

Following this method provides consistency to the qualification of visual inspection processes: a new inspector who passes the qualification can be considered capable as compared to the probability of detection baseline. A common correlation, however, could be assumed between "criticality of defect" and "performance of detection." Intuitively, the most critical defects could be expected to be the most detected, a correlation that is unfortunately misguided. Defect criticality is based on patient risk, not on visual attributes that relate to the ease of detection. Conversely, the visual attribute of a defect has no impact on the risk to the patient. A critical defect could be difficult to detect after 10 seconds (or more) of inspection on a black-and-white background, while a minor defect with cosmetic impact could be detected within 1 second of inspection.

In the parenterals industry, it is common to find that inspectors are qualified based on arbitrary performance criteria, often around criticality. The expectation for product to be inspected 100% for critical defects during qualification leads to lowered expectations with decreasing

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criticality (e.g., 80% for major defects). As critical defects are those that potentially lead to patient safety issues, the value of "100% critical defects" may reassure management as well as regulators about product quality. While this is certainly an ideal figure, this approach may lead to bias and side effects, pushing back the intrinsic nature of visual inspection as a probabilistic process. As a result, three situations could potentially put patients at risk, as outlined in **Table 1**.

The first risk is focusing on obvious critical defects while neglecting those that could legitimately impact patients—the risk of bias on defect classification. For example, a defect with a low probability score of detection may not be identified as critical though, in fact, it impacts patient safety.

The second risk is qualifying obvious critical defects that are not representative of all critical defects seen during routine visual inspection. Such a situation may lead to a qualification status that is only relevant for *some* critical defects (i.e., the most obvious with 100% probability of detection), but not to *all* critical defects (i.e., the obvious defects with 100% probability of detection plus those with true probabilistic detection, approximately 70-80% probability of detection). Defects in test sets should be representative of the entire range naturally present in production, according to Section 7.1 of USP <1790>. As the variety of critical defects seen during routine production also encompasses defects with lower detectability, inspectors should be qualified using these defects to ensure they can adequately detect them.

> "Qualification of an inspector is only one part of the qualification program"

The third risk is overconfidence in 100% manual visual inspection as a capable process to remove all critical defects. In the case of AQL failure or customer complaint involving a critical defect, this may lead to the belief that 100% manual visual inspection has failed to efficiently remove these defects. In addition, such a situation may incorrectly address manufacturing incidents where, whatever the process design preventing (or not) the generation of critical defects, 100% manual visual inspection will be considered to act as a safety net to remove them, no matter the pollution level of the batch prior to visual inspection. This approach could lead to the idea that quality is not "embedded into the product," but needs a filter, such as 100% manual visual inspection, to build quality.

Paradoxically, the three situations identified in **Table 1** show that putting the criterion of 100% on critical defects may introduce systemic risks related to the process performance of manual visual inspection. Such an approach does not ensure that an efficient manual visual inspection is in place.

Inspection qualification does not intend to assess the perfect detection of a category of defects, even critical defects. Qualification determines if the inspector has the proper gestures, concentration and pacing, the combination of which allows the inspector to consistently detect defects, whatever their classification and the risk they represent to the end user. Qualification of an inspector is only one part of the qualification program; proper training, with adequate illustrated procedures, dry runs, coaching and mentoring are also key to properly qualifying inspectors.

Possible bias on defect classification, unknown performance of detection for the whole variety of critical defects and possible lack of quality embedded into the product prior to visual inspection indicates the 100% detection criteria on critical defects is likely not as ideal as common sense expects.

Conclusion

Even though the detection rate should be as high as possible, the goal of ensuring patient safety does not equal 100% detection of critical defects, neither during routine processing nor operator qualification. It implies something quite different—zero critical defects in the finished product. Visual inspection, with its intrinsic limitations, even on critical defects, is only one piece of a holistic process that requires a

Table 1 Three Situations Where 100% Detection Leads to Greater Risks

	Because of…	…there is a risk of…	…leading to…
Situation 1	Critical defects remaining probabilistically detected	Defects with potential impact on patient safety are not classified as critical, as the detection method cannot ensure 100% detection	Bias on defect classification
Situation 2	Obvious critical defects qualified that are not representative of all critical defects	Qualification status being relevant for only some critical defects	Unknown performance of detection for a variety of critical defects
Situation 3	Overconfidence and misbelief on the purpose of the visual inspection process, with 100% detection routinely expected	Consideration of 100% manual visual inspection acting as "filters" or "safety nets"	Lack of embedded quality into the product, regarding critical defects, prior to visual inspection

robust control strategy of prevention and management of defects, from incoming material to fill-finish steps.

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5.0 Ways Quality 4.0 Will Improve Manufacturing

Snehal Srikrishna, Veeva Systems

Pharmaceutical quality and manufacturing teams will face two significant challenges in the coming year.: drug shortages and rising new types of complex therapies, such as precision medicines.

Recently, the U.S. FDA Task Force on Drug Shortages shed light on the impact quality has on drug supply. It found that nearly two-thirds of 163 drugs that went into shortage between 2013 and 2017 were a result of supply disruptions associated with manufacturing or quality problems ***(1).***

To the second point, complex therapies are typically produced in smaller volumes and their delicate requirements for care create difficulties along the supply chain. Traditional drug manufacturing processes are not suited for these highly individualized medicines.

Quality 4.0—the digitalization of quality management through technologies that increase operational efficiencies, product quality and patient safety—provides the foundation for addressing both drug shortages and precision medicine production. With Quality 4.0, companies adopt advanced, digital systems to streamline and automate processes, connect global partners and suppliers, and enable agility that's so crucial to succeed in a changing regulatory environment.

Despite the tremendous potential and the importance of quality on drug supply, only 13.8% of companies have started their Quality 4.0 journey ***(2).*** Some organizations are paralyzed not knowing how to get started on the path to Quality 4.0 or the right technologies to adopt. Making this first decision is critical to maintaining the pace of innovation and getting medicines to patients quickly.

Here are five top advantages that Quality 4.0 can bring to the life sciences industry.

1. Increased Scalability to Meet Changing Regulations

The only constant in the regulatory environment is change, yet life sciences companies are limited by rigid legacy systems that cannot adapt easily. With Quality 4.0, however, companies benefit from flexible applications that are easily reconfigurable without having to revalidate the entire system. These technologies are also designed for continuous uptime to respond faster to change, reduce risk, and stay compliant.

Cloud-based technologies also bring new regulatory rules and guidance updates from across all 180 countries globally directly into a quality system so manufacturing teams can respond to updates in real time. This seamless connectivity even affords companies the extra time to carefully determine whether a new regulatory rule impacts their specific production line or if they want to set a higher standard than the regulation requires because it impacts quality and patient safety.

2. Greater Visibility of Risk Across Product Lifecycle

Most companies still operate in silos and implement disparate systems across different areas of the business. This limits both visibility and collaboration across the enterprise. Quality 4.0 connects systems and processes to provide greater transparency across the product lifecycle and enable smart decision-making and resource allocation. One area where this has a significant impact is audit management.

With a quality management system connected with other related systems (i.e., quality risk management tools and training applications), manufacturers can define the most pertinent CAPAs to holistically address all related audit findings and connect this information to the training curriculum. Further, by connecting audit findings with quality risk management, companies can proactively manage their overall risk profile to meet the evolving expectations of regulatory agencies. This gives companies a clearer understanding of risk upstream during clinical manufacturing and how to make sure those risks don't become problems downstream during commercial manufacturing.

3. Increased Agility on the Shop Floor

The shop floor is ripe for digital transformation. Manufacturing operations are still mostly paper-based, with aging systems in use long past their shelf life. Adopting new processes for manufacturing or testing methods to meet higher quality requirements is often challenging because of manual processes and rigid systems in silos. Without the implementation of modern technologies that enable digital distribution of procedures and work instructions, it is hard to keep information current when sites or manufacturing lines need to make updates and changes to produce new products.

Quality 4.0 empowers companies to modernize manufacturing operations with advanced mobile applications that can bring workstations online and significantly improve agility and efficiency, while maintaining compliance. With a connected shop floor, facilities can support 24/7 manufacturing and gain real-time visibility for smarter decision-making. Important information is always accessible to operators, even for offline viewing. Synchronizing content onto mobile tablets at each work station also allows operators to quickly access correct information at the point of need to perform their jobs efficiently.

4. Connecting the Manufacturing Ecosystem

Paper-based processes and legacy systems create many business gaps between manufacturing, quality management and content management systems, making it challenging to effectively deliver quality products. Quality 4.0 brings together these complementary systems for a more holistic view and seamless execution.

Connecting end-to-end processes across the manufacturing ecosystem helps resolve issues faster. For instance, when a manufacturing execution system detects a potential nonconformance, it can immediately send the information to a quality manage- ➤

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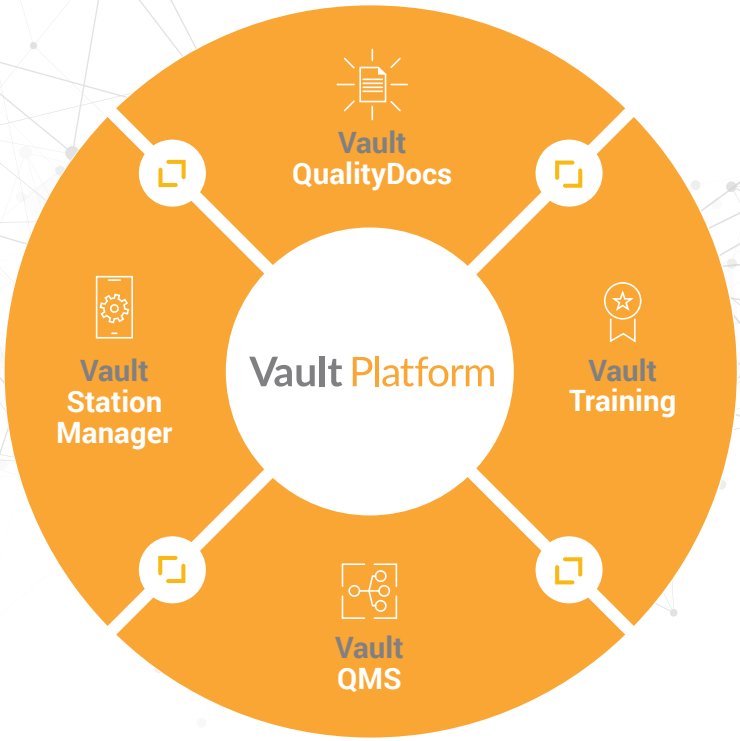

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ment system (QMS). This enables rapid detection, triaging and remediation of non-conformances. Additionally, connecting the QMS to the content management and training systems enables timely push of appropriate content into operators' training curriculum to reduce the incidence of similar non-conformances in the future.

5. Improved Collaboration with Global Partners and Suppliers

Many life sciences companies struggle to work with suppliers and leverage the expertise of external partners worldwide. This is particularly problematic when developing precision therapies and rare disease medications that often involve an expansive network of partners and suppliers that need to work together and bring these innovative therapies to patients.

Unified systems increase transparency across all parties for greater collaboration between employees, suppliers, and contract partners such as CDMOs. As an example, modern systems allow pharmaceutical manufacturers to automate supplier qualification processes and effectively manage supplier corrective actions (SCARs). Linking SCARs to related deviations from incoming raw materials from the supplier can reduce risk of releasing batches and also save time when evaluating suppliers for future products

The Future of Manufacturing

Quality 4.0 is starting to become a reality in pharma manufacturing as companies adopt solutions to enable agility while improving operational efficiency and product quality. The technologies fundamental to Quality 4.0 initiatives provide real-time visibility across content, data and quality management processes for better tracking and more meaningful and actionable insights.

Next generation solutions that emphasize flexibility, connection and visibility position manufacturers for success in the years ahead. Eliminating siloed systems in favor of streamlined Quality 4.0 applications allows for stronger collaboration while enhancing compliance and end-to-end control. This is the key to meeting the new demands of quality manufacturing and support innovation in a new area of medicine.

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The PQL Team Part II: Getting Ahead

Stephan Krause, PhD, Mariam Khan, Callum Chapman, Rob Gaglione, Andy Spasoff and Anthony Mire-Sluis, AstraZeneca Biologics

[Author Note: Part II of this series outlining AstraZeneca Biologics' Product Quality Leader (PQL) Team shows how to employ a capability/skills matrix to both track and existing skillsets. Part I covered the creation of the PQL role and appeared in the January/February issue**.]**

Soon after initiating the PQL role and building a team of PQLs, a capability/skills matrix was developed to help them succeed and grow. The primary objective was to raise awareness among PQL team members and management of the group's current strengths and where gaps may exist.

Inspiration came from PDA's experience using a capability/skills matrix to track the knowledge and levels of experience in key competencies of members in the PDA Biotechnology Advisory Board (BioAB). PDA wanted to see if the existing experience of BioAB members aligned with the Association's long-term strategic plan. For most of its existence, BioAB has been capturing capabilities (knowledge/experience levels) for individual team members. This data is periodically updated and reviewed to align with PDA's long-term vision and strategic plans.

By focusing specifically on PDA's planned areas of future growth, BioAB has deliberately used the available data on member capabilities to identify strengths and gaps. This has facilitated the establishment of appropriate priorities by anticipating which future deliverables were achievable and which were more challenging. Regarding gaps, PDA made strong efforts to recruit subject matters experts from across the industry and regulatory agencies to fill these gaps.

> **Practical descriptions for all conditions were established, aligning with each capability or skill level**

Using this capability matrix has contributed to the long-term success of BioAB's ability to support PDA.

Transferring this concept to the PQL team has enabled the team to prioritize, based on gap/risk impact, and to develop extensive training and skill-building in areas where expertise is lacking.

Table 1 illustrates a simplified capability and skills matrix devised for members of the PQL team. Capability is scored and captured for (general) therapeutic areas and elements of manufacturing science of interest based on the established PQL review responsibilities and the current/expected diverse product portfolio. This is listed in the second column of the table (in light brown color). Column 3 (in light green) shows more specific PQL skills for direct tasks requiring review. While the more general capability areas were scored with three levels only (0%, 50%, 100%), a total of five levels (0%, 25%, 50%, 75%, and 100%) were used for specific review skills.

Practical descriptions for all conditions were established, aligning with each capability or skill level. All PQLs used this information score themselves. These "raw ➤

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17 Quality and Compliance – Management for Virtual Companies
17 Technical Report No. 48: Moist Heat Sterilizer Systems: Design, Commissioning, Operation, Qualification and Maintenance
17 Technical Report No. 54: Foundations of Quality Risk Management
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- **23-24** Mastering Automated Visual Inspection
- **23-24** An Introduction to Visual Inspection: A hands-on course

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- **24** Interest Group Meeting Vaccines
- **24-25** Environmental Monitoring and Contamination Control
- **24-25** CMC Regulatory Compliance for Biopharmaceuticals
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Table 1 Simplified Capability and Skills Matrix for PQL Team and Individual Members

PQL Staff	(General) Therapeutic Areas & Manufacturing Science									Specific PQL Review & Approval Areas											
PQL Leader (n=1) and PQLs (n=10)	Small Molecules	mAbs	ATMPs	Antibody-Drug Conjugates	Vaccines	Biosimilars	Combination Products	Medical Device	DS Manufacturing	DP Manufacturing	CQA Development	CMO/Partner Relationship	Quality Risk Management	Deviation Product Impact	Process Validation	TT Clinical	TT Commercial	Comparability	Expiry Dates	DS/DP Specifications	Temperature Excursions	Stability	Reference Standard
Scoring Description for Capability/Skills for Each PQL and all Individual Areas (0–100%)																							
0%	No practical knowledge/experience										Not trained on relevant procedures, guidance, job aids, etc.												
25%	N/A										Partially trained on relevant procedures, guidance, job aids, etc.												
50%	Solid knowledge/experience										Fully trained on relevant procedures, guidance, job aides, etc.												
75%	N/A										Proficient in executing specific PQL review/approval task(s)												
100%	Advanced knowledge/expert level										Experienced in executing specific PQL review/approval task(s)												

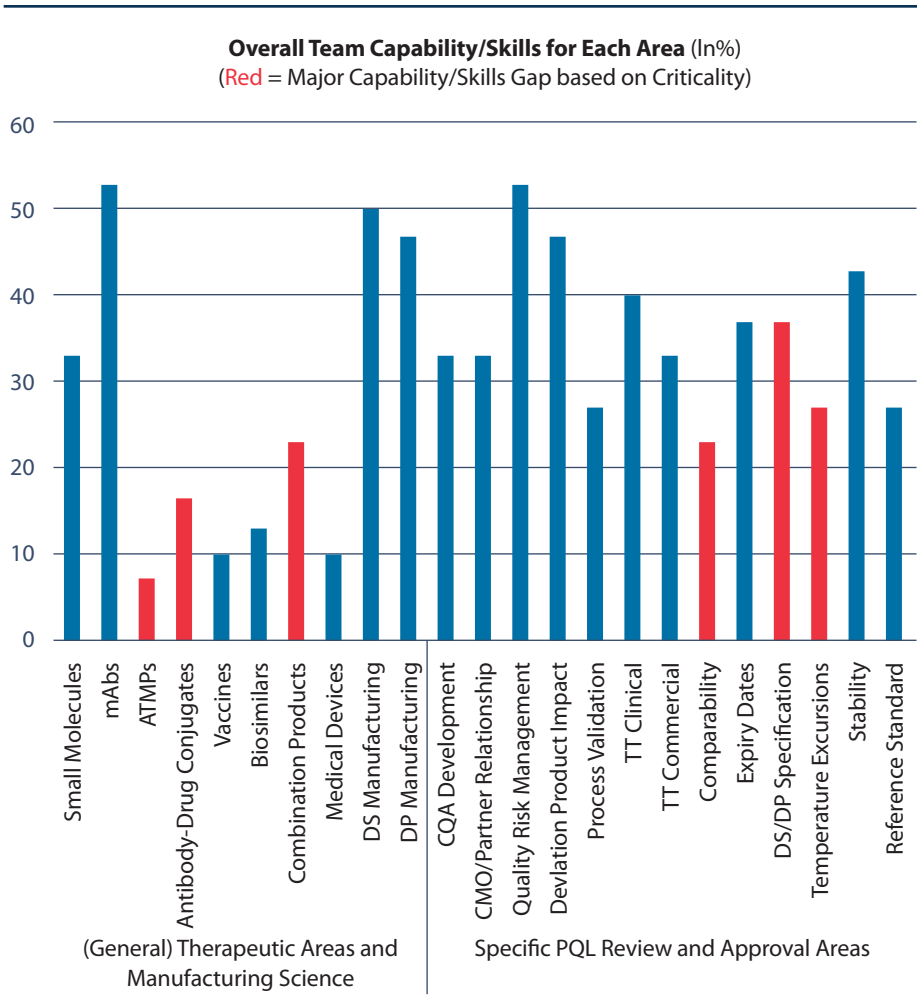


Figure 1 Initial Team Capability/Skills Scores (in %)

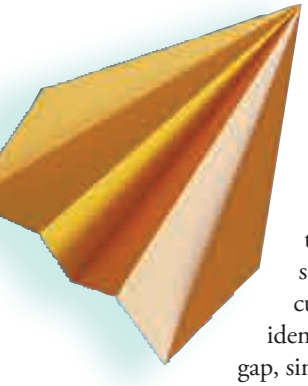
data" scores were then used to capture truly representative data for each team member. Several major criticality factors, such as expected frequency of review events, based on current available product portfolio information, were then used as gap multiplication factors. Below is the list of criticality factors (calculations not shown here):

Criticality (Gap) Factors for Consideration of Scores for Team and Individuals

- Number of expected reviews based on current product portfolio
- Proportion of products in current portfolio
- Assigned product priority
- Reliable internal consulting available

Figure 1 shows the initial overall team capability/skills scores for major review tasks in 2018. The sum of all "raw scores" of each team member represented an overall team score. Each sum was treated with the preestablished criticality factors and thresholds. The results clearly reveal that, within the general capability area, the overall experience level of the PQLs in manufacturing of monoclonal antibodies (mABs) is sufficient (> 50%), while the experience level within the advanced therapeutic medicinal products (ATMPs) is clearly a major capability gap given the

Management now has up-to-date knowledge of its function capabilities



existing team experience and criticality factors (only 7%, in red color). Within the specific skills, the review task of resolving temperature excursions for product in current distribution was identified as a major skill gap, since it was a new review task and these events happen relatively frequently as product is shipped and stored at many different global sites. With time and focused learning progressing, individual and team capability/skill levels are expected to increase faster in the specific review areas.

Periodic evaluations and updating of the capability/skill scores can be conducted relatively quickly and can now support PQL assignment changes whenever needed. In time, the expected increasing capability/skill scores for individuals and the overall team will be measured against short- and long-term function goals.

Management now has up-to-date knowledge of its function capabilities and can quickly adapt to expected and unexpected changes. For example, product portfolio and/or priority changes, such as a push for a highly accelerated product development following an agency-granted breakthrough therapy designation, can now be readily evaluated for impact on existing staff.

Part III will conclude this series by exploring another tool that further refined the PQL role: a Gemba Walk.

About the Authors

Stephan Krause, PhD, is the head of AstraZeneca Product Quality Leader Group. He is a frequent PDA volunteer and current member of PDA's Board of Directors.

Mariam Khan has over ten years of biotech/pharmaceutical industry experience in analytical sciences and quality working on biologics in clinical development. She is currently the PQL on cell therapies and various other monoclonal antibodies.

Callum Chapman is the PQL for multiple molecules across AstraZeneca's pipeline,

Continued at bottom of page 37

Team to Craft PDA Quality Culture Standard

Marilyn Foster, PDA

Development work on BSR/PDA Standard 06-201x: Quality Culture Assessment Tool, PDA's sixth standard, will begin April 20 under the guidance of PDA Chair-Elect **Susan Schniepp,** a distinguished fellow at Regulatory Compliance Associates. This new standard will take the form of a comprehensive quality culture assessment tool and training, designed to guide companies toward a better understanding of quality culture, how to assess it, and what actions to take to improve it.

Fashioned after the assessment tool and training course offered by PDA, companies will be able to use the standard to help collect and measure the verifiable data needed to assess quality at all levels of an organization. The resulting information can then be used to facilitate positive culture changes and support continuous improvement, so the entire organization recognizes the importance of providing patients with high-quality medicinal products.

The expertise of the group members covers a broad range of experience, from quality assurance to engineering to production to global regulation.

For updates on this and other PDA standards, visit the PDA Standards Development website: https://www.pda.org/scientific-and-regulatory-affairs/standards/pda-ansi.

Susan Schniepp

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40 Years of Visual Inspection: Where Do We Go from Here?

Romain Veillon, GSK Vaccines, and John Shabushnig, PhD, Insight Pharma Consulting, LLC

PDA has always been at the leading edge of parenteral visual inspection. Since the early 1980s and the publication of works by **Julius Knapp,** PDA has helped establish contemporary standards for manual inspection and validation of inspection processes.

Nowadays, automated inspection has reached maturity and regulators expect strong baseline standards to assure reliable use of this visual inspection process. The validation process remains difficult, however, and visual inspection and particle control remain an oft-cited regulatory observation and reason for recall.

In coming years, visual inspection is expected to undergo a major advance with the application of artificial intelligence (A.I.) and deep learning technologies. This could enable automated inspection machines to reach previously unmet performance in terms of defect detection and reduced false reject rate. It may also decrease the time required to develop new inspection recipes for specific products. While suppliers are working to integrate A.I./deep learning into their machines, some pharmaceutical companies are currently doing their own pioneering work in developing technical capacity in data science. To date, limited information is available on strategies for the needed validation strategy to support implementation of this new and promising technology. PDA is committed to filling this with a special focus on automated visual inspection and deep learning at this year's *PDA Visual Inspection Interest Group Workshop*

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The PQL Team Part II: Getting Ahead continued from page 33

working mostly with inhaled biologics and advanced therapy medicinal products. He is a UK-registered Pharmacist and is interested in the area where CMC meets clinical development.

Rob Gaglione serves as a lean practitioner for AstraZeneca's Biologics Development Quality Department. Prior to joining AstraZeneca, he worked as a supplier quality professional in the medical device industry.

Andy Spasoff has worked in the biotechnology industry for over 18 years at multiple large companies. He has spent time in Process Development, Global Operations and Quality focused on the commercialization and commercial support of biologic products.

Anthony Mire-Sluis, PhD, is currently Head of Global Quality at AstraZeneca. Prior to working at AstraZeneca, he held the role of Vice President of Quality at Amgen. He was also Principal Advisor, Regulatory Science and Review, Office of Biotechnology Products, CDER and Head of Analytical Sciences and Standards, Office of the Director, CBER, U.S. FDA.

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PDA Responds to WHO DI Draft Guideline

15 January 2020

Dr. Sabine Kopp
Group Lead, Medicines Quality Assurance
Department of Essential Medicines and Health Products
World Health Organization
CH-1211 Geneva 27
Switzerland

Reference: Draft guideline on data integrity (working document QAS/19.819)

Dear Dr. Kopp:

PDA appreciates the opportunity to comment on WHO's draft guideline on data integrity, working document QAS/19.819. We present our comments in the attached table.

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

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

Sincerely,
Richard Johnson
President and CEO

PDA Commenting Task Force

Madlene Dole, Novartis

Kir Henrici, The Henrici Group

Maryann Gribbin, Faith and Royale Consultants

Data Integrity: From the Basics to Big Data

David Hubmayr, CSL Behring

Data integrity is not a new concept, yet global regulators continue to cite manufacturers for deficiencies in this area.

This was my first takeaway as an attendee at the *2019 PDA Data Integrity Workshop* hosted by PDA last September in Washington, D.C. This workshop featured presentations from global regulators and industry leaders covering burning data integrity questions from when does data integrity start to what role mindfulness can play to how to address data integrity involving big data technologies? The speakers provided their own perspectives on why data integrity remains a challenge for our industry and provided their own recommendations to solve this critical issue.

As an attendee, I want to share some of what I learned.

In the first plenary session, "Overcoming Data Integrity Challenges," **Carmelo Rosa,** Division Director, Office of Manufacturing and Product Quality, CDER, U.S. FDA, explained the data integrity expectations throughout a product's lifecycle. As a general statement, it is understood that all data (electronic and hardcopy) generated throughout a product's lifecycle must be accurate, reliable, complete, truthful, correct, and unaltered. This includes data generated during clinical and pre/post approval stages. Of course, understanding, interpreting, explaining or signifying certain data generated (e.g., unexpected/out-of-specification results) may depend on the phase in which it was generated (e.g., if results were generated during early clinical/process or product/method development stages).

The inclusion of data from clinical stages is one area that currently requires more attention. In fact, documentation of the develop process is often neglected as it is not specifically audited. Many firms fear not having a "perfect story" during these early phases. Rosa emphasized, however, that regulators do understand that data evolves throughout early phases. Still, data should never be falsified, altered and/or manipulated to misrepresent information. This includes, but is not limited to: lack of controlled access to computer systems, "trial" HPLC injections of samples outside/within a quality structure, not recording activities contemporaneously/backdating, fabricating/falsifying batch records, copying existing data as new data, deleting results with no justification and retesting samples to present better results.

GMPs apply to all Phase II/III stages once the drug is available, including exhibit batches, validation phases and commercial batches. If a process or analytical method under development that may require modifications to equipment parameters and settings, as well as formulation, these should be documented and explained. Regulators will ask for the full development story, including data integrity, as they want to be confident that the drug is safe for patients.

Following Rosa's presentation, **Els Poff,** Executive Director, Data Integrity Center of Excellence, Merck & Co., explored the challenges surrounding the transition from paper to digital. While a fully digital future presents much promise, data integrity challenges center around technology, people/culture and regulatory requirements. Technology challenges include lack of fully data integrity compliant instruments/systems/solutions, the risk of going backwards and cyber threats. People/Culture challenges include the still inherent resistance to change, entrenched legacy ways of working, adequate socialization (the why message), being trapped by the responsibility of daily operations, pace of execution, capacity to execute, return on technology investments and production scheduling demands. And last but not least, regulatory challenges include revalidation efforts, differing global regulatory expectations and impact on filings.

One possible solution for overcoming these challenges is to bridge traditional paper-based approaches and fully digitized

Miss the *2019 PDA Data Integrity Workshop?* PDA will be hosting another workshop on data integrity, Sept. 16–17, in Washington, D.C.

To learn more about the *2020 PDA Data Integrity Workshop* and to register, visit the workshop home page.

https://www.pda.org/2020diworkshop

environments with a hybrid system. Evolution, without disruption, will be long. The risk of falling behind the curve must be balanced with adequate controls and protection from cyber threats.

Being Mindful of Data Integrity

The second day of the workshop featured a breakfast session on the connection between mindfulness and data integrity with a presentation from **Amy L. McLaren,** Senior Director, Quality and Compliance, and **Julie C. Maurhoff,** Senior Director, GxP Compliance, both of Ultragenyx Pharmaceutical. They suggested that when thinking of data integrity, consider the second word, "integrity."

"Integrity" can be defined by the state of being whole and undivided while paired with mindfulness. Living mindfulness in everyday work and private life provides us with enhanced clarity, helps us focus and supports us in problem solving through critical thinking. But management has to set the tone. Enough "space," such as understanding of time constraints, trust, motivation, etc., must be provided to staff to make patient-focused decisions with available data.

Big Data: Fact versus Fiction

The closing session explored the impact of big data on data integrity. Since this is a new technology for us, I thought it was great to separate fact from fiction with insights from presenters, **Mark A. DiMartino,** Director, Quality Data Sciences, Amgen, and **Peter E. Baker,** Vice President, Green Mountain Quality Assurance.

First, the facts. Artificial intelligence (A.I.) applications augment human intelligence and can improve products and processes. When combined with data science-driven solutions that leverage data, insights can be efficiently found. This means ensuring data access, applying appropriate analysis methods to unlock information. All of this leads to meaningful visualization and interpretation of information. At this time, multiple tools are commercially available.

On the fiction side, A.I. can explain its decision making as A.I. software can make recommendations or take action based on its knowledge, but it cannot break down its decision-making process to explain how it came to those recommendations. Also, consider goal setting. There is the growing fear that A.I. technologies define their own goals. What does this mean? People should define goals; technologies should execute them. Technologies should not be leading execution of goals.

From this workshop, I took away that data integrity must be taken into consideration right from the very beginning and mindfulness can lead to enhanced clarity. New technologies offer great opportunities for companies, and, by extension, patients but data integrity remains a consideration no matter the technology.

About the Author

David Hubmayr is member of the Integrated Commissioning and Qualification Expert Group at CSL Behring. He is responsible for qualification compliance.

CCIT Challenges for Cryopreserved Biologic Products

Pascal Sircoulomb, ARaymondlife, and Luce Sohier, SCHOTT

[Editor's Note: The study below was jointly conducted by ARaymondLife and SCHOTT**.** Once more long-term data is available, both authors may consider submitting to peer review at a later date**.]**

Cell and gene therapy products are typically stored at -180°C and -80°C, respectively, throughout their lifecycle to provide a safe environment to the drug substance and prevent degradation, but such extreme cold temperatures can negatively impact vial-based container-closure systems.

While cryopreservation keeps the product in a stable state, allows for a longer shelf life, and ensures stability throughout the supply chain, manufacturers must plan for the unique challenges for vial-based container closure systems.

For example, primary packaging components, such as glass vials, rubber stoppers, and aluminum seals, exhibit contraction during cryogenic storage due to differences in their thermal expansion rates. The contraction of primary components at cryogenic temperatures in conjunction with individual component defect(s) and improper component assembly/compatibility can potentially lead to leakages and/or container closure integrity (CCI) failures.

Typically, in a system where the vial is closed with an aluminum crimp and a rubber stopper, the rubber stopper can deform and maintain the system's integrity. However, at temperatures below the glass transition of the elastomer (Tg about -50°C), the stopper becomes glassy solid. Then it is crucial to verify if the system retains its integrity ***(1).*** In fact, a few cell and gene therapy companies have had to recall their products due to container closure integrity failures, as primary packaging component compatibility was not established ***(2).***

Therefore, there is a need to have a validated container closure system to maintain container closure integrity during storage of these products.

A recent study analyzed a push-fit cap system produced by ARaymondLife combined with rubber stoppers at -80°C to test if this system would fall under USP <1207> Package Integrity Evaluation - Sterile Products. This USP chapter provides guidance in package integrity (leak) testing to ensure that the given package protects the filled sterile pharmaceutical product and meets all physicochemical and microbiological label-claimed specifications through expiry, i.e., sterility preservation, formulation loss preservation, and critical gas headspace preservation. The analysis also fell under USP chapters <1207.1> Package Integrity Testing in the Product Life Cycle - Test Method Selection and Validation and <1207.2> Package Integrity Leak Test Technologies, both

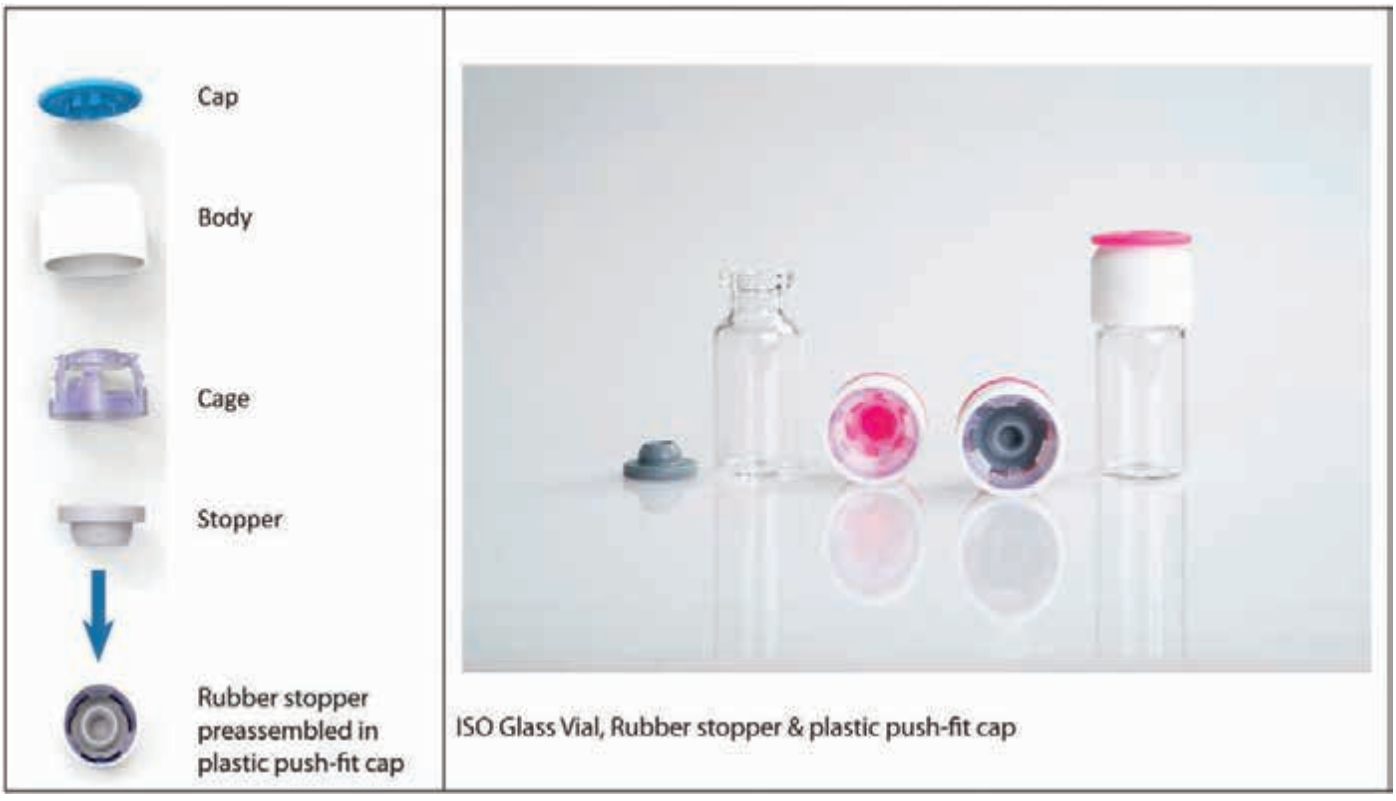

Figure 1 Overview of Primary Packaging Components

> **manufacturers considering switching from aluminum caps should also evaluate the combination of all the components**

of which provide a guideline for container closure integrity test method selection and testing technologies.

Although, several CCIT methods (deterministic and probabilistic) are available for container closure systems as per <1207.1> and <1207.2>, helium leak test and laser-based headspace analysis methods have been routinely used for detection of submicron leaks ***(3–5).***

The study included the following primary packaging components as outlined in **Figure 1** as well as the following CCIT instruments and study conditions:

Glass vials: SCHOTT Fiolax® 2R and 6R ISO designs (hereinafter designated as ISO vials) representing 13 mm and 20 mm crown diameters, respectively.

Rubber stoppers: Suppliers A and B in 13 mm and 20 mm crown diameters.

Closure: RayDyLyo® CTO13 & CTO20 (hereinafter designated as plastic push-fit cap) and flip-off aluminum caps with 13 mm and 20 mm diameters.

A headspace oxygen analyzer served as the container closure integrity test instrument. This instrument was calibrated, and performance checked for accuracy (NIST-traceable oxygen standards) and precision (ten consecutive measurements of a sample) at T_0 and at each time point. The plastic push-fit cap and the stopper were sterilized using gamma irradiation. Unfilled samples (n = 10 for each configuration) were purged with nitrogen prior to capping with plastic push-fit caps or crimping with aluminum seals. The evolution of oxygen level in the headspace was measured at room temperature for T_0 and each subsequent time point of the study (see **Figure 2**). Incubation was -80 ± 2°C (real time). Time points were six months, one year and two years. Further long-term studies are in the process of being performed for 3 years as well.

Oxygen ingress data on 2R samples (13 mm) stored at -80°C

As shown in **Figure 3,** the 13 mm vial system samples, with gamma-sterilized stoppers, stored at -80°C, did not show any significant ingress of oxygen in the headspace within a year of storage, indicating that CCI is maintained during this time period. ➤

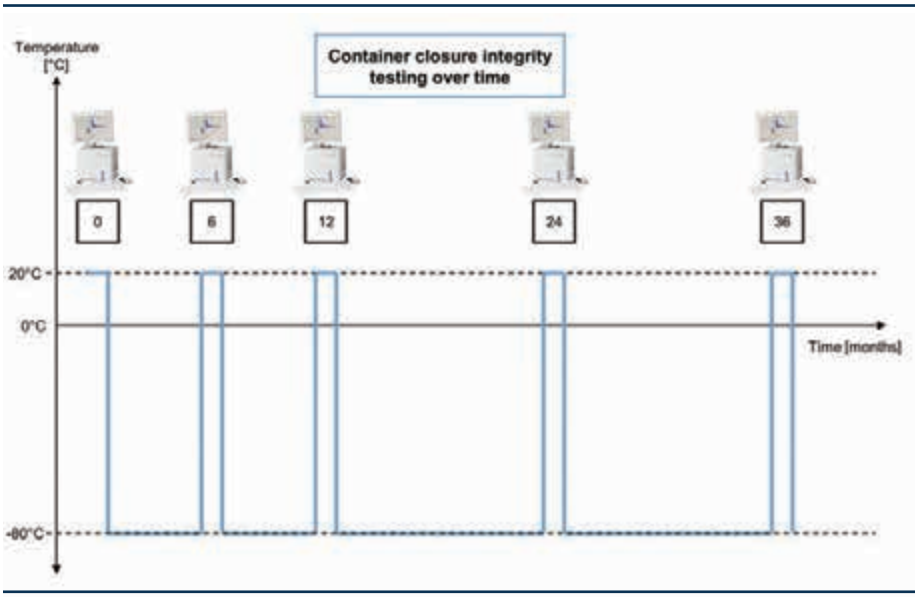

Figure 2 Overview of the Container Closure Integrity Test Protocol Over Time
(The oxygen level in the headspace was measured at room temperature for each time point of the study. After the measurement, the samples are stored at -80°C again.)

The results were:
Stopper A and a plastic push-fit cap showed an average ingress of 0.12% atm at T0 and 0.08% atm after one year

Stopper B and a plastic push-fit cap showed an average ingress of 0.08% atm at T0 and 0.15% atm after one year

Stopper A and an aluminum cap showed an average ingress of 0.15% atm at T0 and 0.15% atm after one year

Stopper B and aluminum cap showed an average ingress of 0.10% atm at T0 and 0.13% atm after one year

Oxygen ingress data on 6R samples (20 mm) stored at -80°C

Similarly, the 20 mm vial system samples, with gamma-sterilized stoppers, stored at -80°C, did not show any significant ingress of oxygen in the headspace within two years of storage, indicating that container closure integrity is maintained during this time period (**Figure 4**).

The results were:
Stopper A and a plastic push-fit cap showed an average ingress of 0.24% atm at T0, 0.19% atm after one year and 0.23% atm after two years

Stopper B and a plastic push-fit cap showed an average ingress of 0.17% atm at T0, 0.11% atm after one year and 0.18%atm after two years

Stopper A and an aluminum cap showed an average ingress of 0.25% atm at T0, 0.15% atm after one year and 0.21% atm after two years

Stopper B and an aluminum cap showed an average ingress of 0.20% atm at T0, 0.13% atm after one year and 0.17% atm after two years

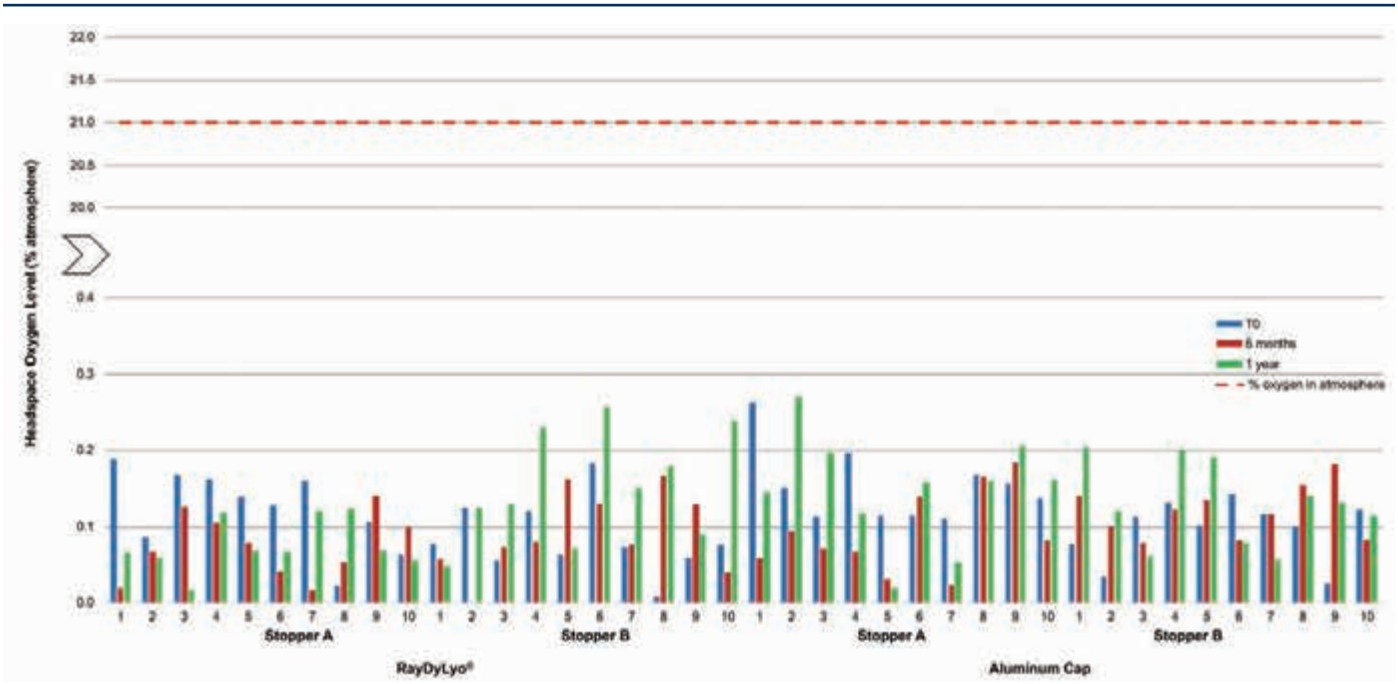

Figure 3 Average headspace oxygen level of CTO13 gamma sterilized samples at various time points after storage at -80 ± 2°C. The red dotted line indicates the maximum oxygen level possible in the atmosphere.

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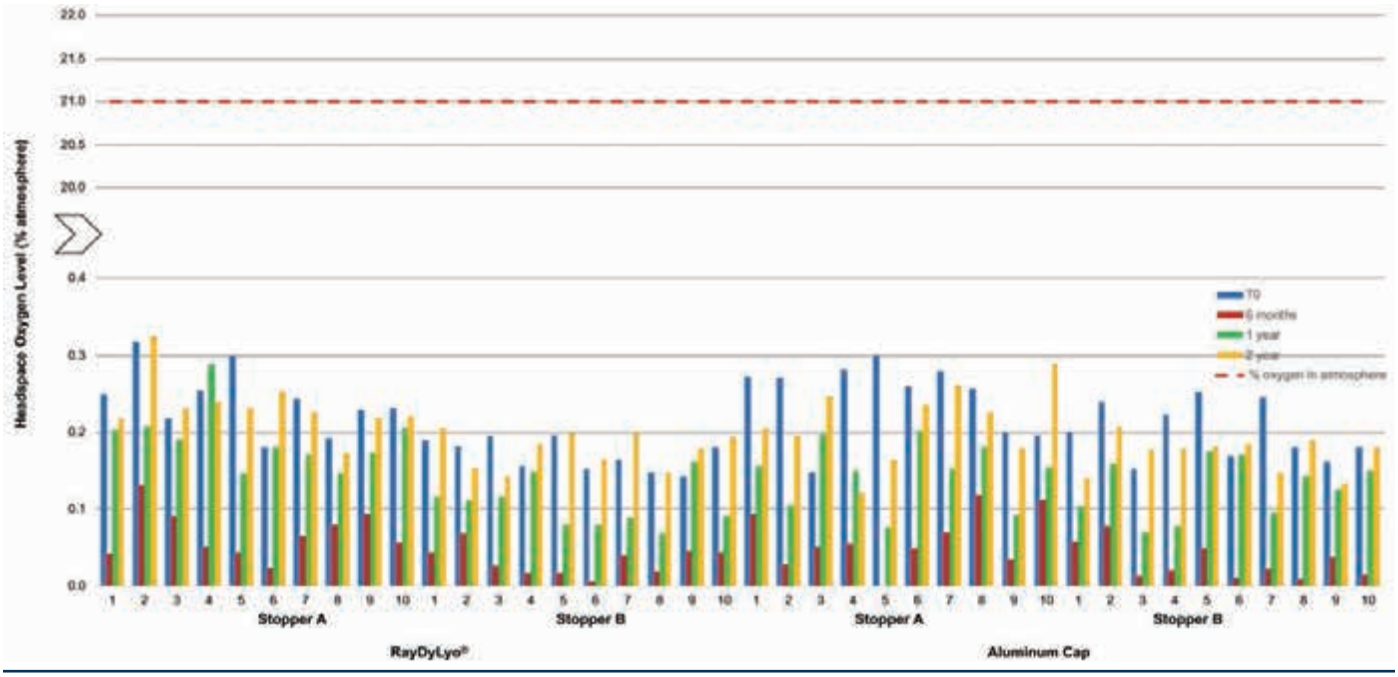

Figure 4 Average headspace oxygen level of CTO20 gamma sterilized samples at various time points after storage at -80 ± 2°C; The red dotted line indicates the maximum oxygen level possible in the atmosphere.

Conclusions

When evaluating the storage of product at -80°C, it is important to select a suitable container closure system for the secured storage of gene therapy products at cryogenic temperatures. These results of this study suggest that the two types of vials (2R and 6R) in combination with the tested stoppers and plastic push-fit caps (RayDyLyo® CTO13 and CTO20) can safely store product at -80°C. Plastic push-fit caps show reliable results, maintaining container closure integrity for a period of at least one year at -80°C, offering an alternative sealing system to traditional aluminum caps.

Still, manufacturers considering switching from aluminum caps should also evaluate the combination of all the components using the available capping equipment under normal conditions of use.

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About the Authors

With 30 years of experience in the field of medical devices, in-vitro diagnostic and pharmaceutical packaging, **Pascal Sircoulomb** has been holding sales, marketing and management positions within large international companies (BD, Danaher/Leica) as well as start-up biotech firms. He joined ARaymondlife in 2018 as Business Development Director

Luce Sohier holds a five-year degree diploma in biochemistry and microbiology from the University of Nancy, France. She has worked in upstream processing in a collaboration with Merck Millipore and Pall, and downstream processing with West and SCHOTT. Currently she is in charge of business development for sterile solutions at SCHOTT in Europe.

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Could A.I. Optimize Visual Inspection?

Andreas Gross, Syntegon

Visual inspection is a challenging stage in the pharmaceutical manufacturing process. This is especially true for products with difficult characteristics, such as highly viscous parenteral solutions where air bubbles cannot be completely eliminated, making it problematic to differentiate them from particles. Those cases usually require long development and optimization times for vision algorithms before achieving a balanced operational level of detection versus false reject rates.

Artificial Intelligence has the potential of shortening this development period and optimizing the desired results more quickly—a classic win-win situation for both pharmaceutical manufacturers and patients, who ultimately receive high-quality products.

Photo courtesy of Syntegon

There are many successful automated inspection techniques on the market that enable very high detection rates, such as individual spin units to prepare the product before inspection, high resolution digital cameras and the static division light transmission method. Nevertheless, in some cases the combination of dense solutions with small containers does not promote the movement of particles, which leads to reduced detection probability. Moreover, agglomerations or other types of inherent morphological features that are similar to particles and bubbles resembling glass particles can cause false rejection of good containers. And every single false reject is one too many, particularly for high-cost products. A.I. applications have the potential of further increasing detection rates and decreasing the number of false rejects in difficult products like dense and bubbly solutions.

While many pharmaceutical producers and machine manufacturers are considering the use of A.I., reservations about implementation and validation are keeping most companies from using these applications in real production environments. In parallel, machine vision software companies are already offering deep learning vision tools as part of their portfolio. Hence, it is not always necessary for manufacturers of automated vision inspection machines to develop their own deep learning algorithms or neural networks. In fact, the existing solutions only require moderate software modifications. Additionally, an upgrade of the vision computers with higher processing power can be realized with graphic processing units (GPUs), which are widely available in the gaming industry.

When it comes to validation, in contrast to many other industries, the deep learning model must be "frozen" once the development phase is finalized. It must be static and can no longer change to make it version-controlled for validation. A recent discussion paper published by the U.S. FDA about the regulatory framework for Software as a Medical Device (SaMD) provides a good reference for application in areas different from pharmaceutical production ***(1).***

No "One-Size-Fits-All" approach

Typically, a one-size-fits-all approach will not work when using deep learning for visual inspection. Instead, the first step should consist of a preassessment based on a large number of diverse images from reference samples. For example, this could be images of good units with bubbles, different stopper positions, products and fill volumes for body inspection and various types of particles intrinsic to the process. Based on the available image data, offline verification studies provide the basis for the integration of deep learning models into the existing software. In the second step, a customer-specific project should be defined with parameters such as product, existing machinery, expectations and timeline.

Figure 1 compares the standard recipe development and validation (left) to the deep learning method (right): the principle process does not change, and the recipe parameters are still validated according to GMP requirements. The only changes are the tool used to develop the process and the required hardware. As mentioned above, even the hardware ➤

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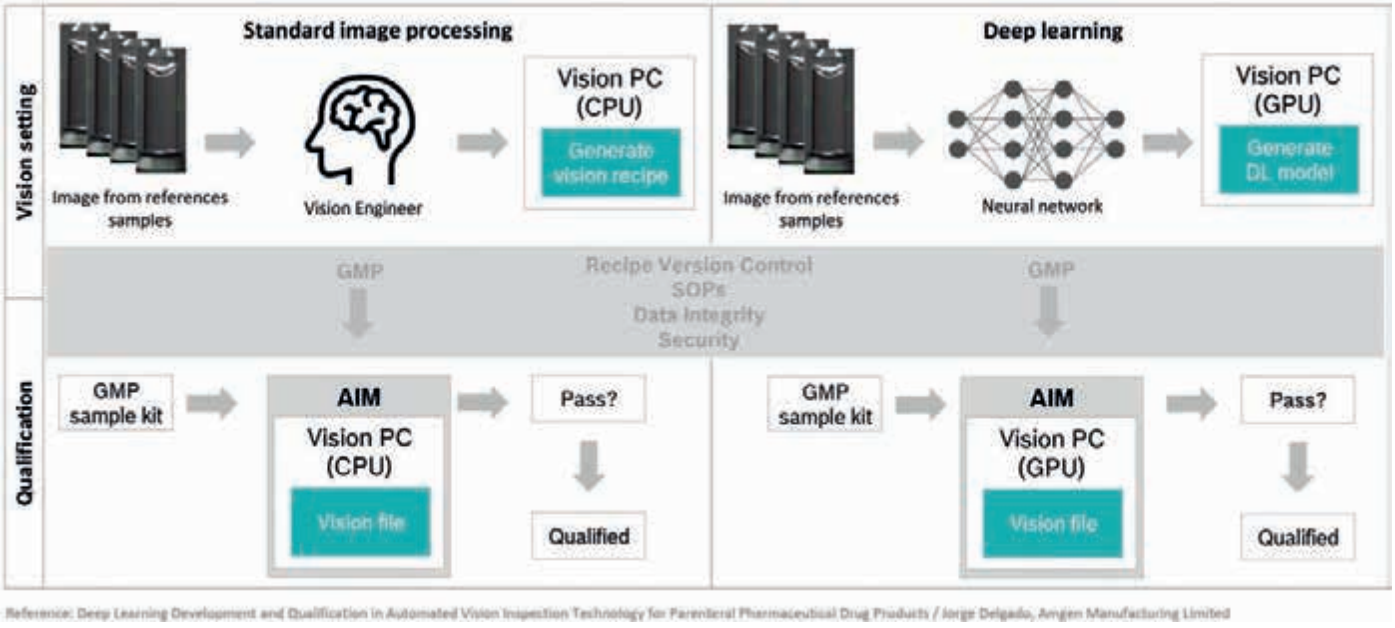

Figure 1 Standard and Deep Learning image processing

(Deep Learning Development and Qualification in Automated Vision Inspection Technology for Parenteral Pharmaceutical Drug Products / Jorge Delgado, Amgen Manufacturing Limited)

only changes slightly: Deep learning requires PCs with GPUs capable of processing complex and massive amounts of data. In a deterministic deep learning model, small packages are trained up to a certain "level of intelligence" and then frozen. This is especially important regarding validation, regulatory approval and inspection.

> "A.I. could potentially become a trendsetter for the pharma industry"

A.I. a Potential Trendsetter

USP <1790> Visual Inspection of Injections specifies that "validation of the automated inspection equipment should be based on comparison with the compendial manual inspection process with an expectation that alternative inspection methods demonstrate equivalent or better performance." This is definitely true for the current state of deep learning in visual inspection. A.I. could potentially become a trendsetter for the pharma industry as it improves the current practice of visual inspection.

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Upsizing Manufacturing for Gene Therapies

Rebecca Stauffer, PDA

CBER Director **Peter Marks** compared the current state of manufacturing for individualized gene therapies to the drink sizes at a coffee shop in his introduction to the public workshop, *Facilitating End-to-End Development of Individualized Therapeutics,* held March 3 at the U.S. FDA headquarters in Silver Spring, Md.

"We are still making vectors much the same way we made them at the turn of the millennium, and we really need to figure out how to move that forward," he said.

"Right now, we have one sweet spot, which is the 'grande' size." (For those unfamiliar with the "grande" size used at one of the world's largest coffeeshops, it is ironically the "medium" of the three sizes offered.)

According to Marks, manufacturers of individualized gene therapies are currently capable of producing between 100 and 10,000 batches a year, equated to mid-level manufacturing. To achieve large-scale manufacturing, they need to produce more than 10,000 batches. Unfortunately, he noted, "the technology is simply not there."

During a session dedicated to manufacturing issues, two leading experts in the field of individualized gene therapies offered their insights, including potential solutions to the challenges they face.

Guangping Gao, PhD, University of Massachusetts Medical School, explored the manufacturing of adeno-associated viral (AAV) vectors in his talk, "Challenges and Opportunities in Development and Manufacturing of Individualized Therapeutics with AAV Vector-Based Gene Therapies." Dr. Gao is one of the leading researchers studying the potential for AAV vectors to cure patients suffering from the genetic, degenerative neurological disorder Canavan's disease. This rare disorder commonly affects infants, who lose their motor abilities over time and, most often, do not live past childhood.

When it comes to manufacturing, the number one hurdle is getting the therapy to patients.

"I do not think we have enough vectors to treat patients for a commercial drug," Gao said. A need for vectors with high enough potency to develop an effective treatment remains problematic. While advancements have been made at the clinical level, commercial-scale is still a high bar for these therapies.

As for a solution, high-throughput sequencing is one way that additional vectors are being located.

"We still have room to improve our vectors," he emphasized.

Current AAV manufacturing platforms generally rely on two different approaches: transfection-based and infection-based. Transfection-based approaches, which involves inserting genetic material directly into a cell, have proven quite popular. Infection-based approaches, as indicated by the nomenclature, involve infecting a line of cells with an adenovirus. Gao showed data indicating that certain infection-based approaches using baculoviruses and HELA cells are gaining in popularity.

Other major manufacturing challenges for AAVs include the gap between producibility and need, scaling up bioreactor-size versus yield-per-cell, technology transfer, costs and storage and distribution.

Jason J. Gill, PhD, Associate Professor, Bacteriophage Biology and Microbiology, Texas A&M University, spoke about some of the challenges associated with manufacturing phage therapy. In "Development of Phage Therapy: Personalized Medicine and Individualized Therapeutics," he began with an overview. Phage therapies involve using bacteriophages (or "phages") to treat infections. Generally a type of virus, phages were studied through the 1940s as a potential treatment for bacterial infections. The development of antibiotics put an end to those studies, until recently.

Manufacturing phage products requires understanding their biology, he explained. Phages are millions of years old and quite hardy, easily adapting to their hosts, making them very specific. Phages also have a diverse set of genomes. In fact, different phages from the same host can have unique genetic codes. This makes scaling ➤

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up from small, clinical batches to large-scale commercial manufacturing difficult.

Gill sees the development of a phage library as one potential way to offset this challenge. Manufacturers could then "take that through some sort of regulatory process and it [the product] could be widely available and even mass-produced."

At the same time, intellectual property (IP) concerns from companies developing phage therapies would need to be resolved.

"IP protection would help get more investment in the field," he said.

From Individualized Therapies to Individualized Inspections

Next, **Roger Plaut,** PhD, Research Microbiologist and Reviewer, CBER, FDA, and **Anita Richardson,** Associate Director for Policy, CBER, FDA, joined Gao and Gill for a Q&A session open to the audience.

During the Q&A, one audience member asked Gao about the potential for creating a cell line that produces high enough titers to avoid having to perform transfection, as this would improve manufacturing capacity.

Gao replied that there are two major issues with this approach. One, the regulatory protein (the protein that influences DNA molecules) used for AAVs is highly cytotoxic. The second is a lack of knowledge regarding the factors that can improve gene therapy vector production. He thinks a tighter system that reduces protein expression could address both challenges.

Another question was posed about FDA's strategy for inspecting facilities producing individualized gene therapies, particularly if they are made at various different hospitals.

Richardson replied that CBER is currently taking an individualized approach, much like the products and processes being inspected.

"I think that we are looking at those types of facilities on a case-by-case basis, taking all the facts and circumstances and the product into consideration, and also the flexibility needed in this field," she said.

As individualized gene therapies grow in the marketplace, manufacturing will continue to face unique challenges. The *Facilitating End-to-End Development of Individualized Therapeutics* showed that CBER continues to look at progress in this area.

Originally published online March 12, 2020

Inaugural BioManufacturing Conference Tackles Five Issues: Part I continued from page 18

the medicinal product, active substance, excipient and primary container."

The water for injection session focused regulatory changes enabling membrane-based ambient water for injection for biomanufacturing. **Fritz Röder,** Senior QA Manager, Merck KGaA, and **Jochen Schmidt-Nawrot,** Lead Engineer, Process Utilities, CRB Group, discussed this regulatory update and its practical implications for manufacturing companies. They also outlined potential acceptance of other methods in the future.

The session, "From the Drug Substance to the Finished Product," showed that an integrated development approach for drug substance, drug product and the finished product is required to ensure that the quality target product profile is met. To illustrate this concept, the presentations in this session explored the important topics of leachables testing, excipient selection and testing and container-closure capability. It was emphasized throughout these talks that risk-based strategies and modeling approaches, which might be used already in other industries, should be applied to generate the relevant data. **Armin Hauk, PhD,** Lead Scientist E&L, Sartorius Stedim, shared, "The 'Fate of Leachables' in Biopharmaceutical Downstream Processes," showcasing a holistic approach for leachables assessment throughout the entire downstream lifecycle. Thanks to the knowledge acquired on extractable profiles—takeng from state-to-art analytical methods and complete understanding of the manufacturing process and the plastic formulation—the leachable content can be predicted by applying physical laws to each process step. **Adithya Balasubramanian,** Associate Principal Scientist, LONZA, presented on "Degradation of Excipients in Formulations," and **Vivek Thakare,** Principal Scientist, Novartis, shared a case study on investigating drug product and container closure interactions for a diluent containing prefilled syringe.

Facility design was another key topic. Considering the increasing pressure to make products available to patients as fast as possible, there is a critical need for designing facilities able to fulfill the new challenges of novel therapeutics as well as retrofitting existing facilities to produce products in a more efficient way while still achieving the highest quality. **Nihit Singhal,** Team Leader - Process Consulting, Sartorius, provided useful insights and a case study for establishing efficient design in drug manufacturing facilities. He pointed out that process understanding is one of the core success factors of any facility design as a lean and agile structure, now mainly driven by single-use system implementation. **Indu Conley,** Process Engineering Department Manager, DPS Group, shared her experiences creating new facilities and retrofitting existing ones. Experience gathered from many years of projects provides a good framework for steering design towards the most efficient facility.

Finally, **Morcos Loka**, Training Manager, GMP Advisor, Minapharm, provided a methodology to add a new highly potent drug into an existing facility based on QRM. His talk focused on using QRM as an essential tool when introducing a new product into an existing facility in order to assess the risks and verify how those risks are mitigated. Risks can be controlled by a combination of technical controls, e.g., double HEPA filtration and procedural controls such as campaign manufacturing, flushing before disassembly, etc.

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Indah Kusumawardhani

Clinical and Regulatory Development Program Associate | ***Edwards Lifesciences*** |
Member Since **2017** | Irvine, California

What has been your most memorable PDA experience to date?
Serving as the President of the PDA Southern California's student chapter for the 2018–2019 term has been my most memorable PDA experience yet. I had the chance to interact with multiple people from my school, the Keck Graduate Institute (KGI), the Southern California Chapter and multiple industry professionals I met at PDA events. All these individuals continuously kept me inspired to grow the student chapter's presence in Southern California.

Describe a highlight from this experience.
I appreciated the opportunity to represent the student chapter during Chapter Council meetings that featured representatives from PDA chapters across the globe. Many chapters, including the Australia, Pacific Northwest and West Coast Chapters, have asked for our recipe for success as they develop their own student chapters.

It was also an eye-opening experience to see our student chapter, with support from the Southern California Chapter and KGI, be recognized for outstanding programs, positive collaboration with our parent chapter and exceptional member services, becoming a gold standard for student chapters.

How did you learn about PDA?
I got to know PDA through discussions with my regulatory affairs professor who happened to also be involved with PDA. I then made the decision to join after attending several events and learning more about PDA. I found that being involved with PDA helped me attain multiple skillsets, which proved to be very beneficial for my professional development.

Why did you choose this field?
I decided to pursue a master's degree in clinical and regulatory affairs to help me transition from academic research to the life science industry. From my research experiences, I realized that quality and regulatory are essential to ensure compliance with current regulations—an area sometimes neglected. I saw regulatory affairs as a way to act at another level, but still be involved in the huge process of delivering new treatments to patients.

What are some of your hobbies?
I love hiking, traveling and photography!

What is your advice to someone entering the field?
Be a lifelong student who is always curious to pursue personal and intellectual growth.

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Susan Schniepp, Regulatory Compliance Associates

Connect with Others via PDA

The COVID-19 virus has disrupted daily life for everyone. It has changed the way we work and how we communicate. That is why staying connected to our colleagues is one of the most important actions we can take right now. PDA is working to help our community stay up-to-date on COVID-19 and other issues important to our industry. For example, PDA President **Richard Johnson** recently held a free webinar to inform members about PDA's COVID-19 activities and to discuss myths and facts about the virus, including how to protect yourself and others from contracting the disease.

As serious and consuming as this issue is, we all still need to do our jobs, and our jobs involve producing high-quality medicines for patients. Since many people are working from home, we need to take advantage of online networking opportunities to stay in touch and keep current on issues that impact our ability to do our jobs. PDA members can connect with fellow PDA members by:

- Participating in a PDA Connect℠ discussion (community.pda.org)
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You can also access relevant publications including the *PDA Letter* (www.pda.org/pda-letter-portal/home), the *PDA JPST* (journal.pda.org), our library of technical reports in the technical report portal (techpubportal.pda.org) and technical books at the PDA Bookstore. (www.pda.org/bookstore).

PDA has a wealth of information and resources to offer. That includes our staff, who are available to help answer your questions or discuss topics that help drive our industry. PDA encourages you to communicate with your colleagues and expand your network by taking advantage of its many online tools so you can stay connected as we all navigate these transformative times.

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