People • Science • Regulation

PDA Letter

Volume LV • Issue 3 www.pda.org/pdaletter March 2019

Industry Eyes Future of Visual Inspection 20

Valor® Glass—It's About Reducing Particulates.

Enduring quality and reliability to help avoid recalls and regulatory action.

Quality is critical in patient care and drug manufacturing. Particulate contamination is a common problem found in today's parenteral drugs. Valor® Glass' low coefficient of friction significantly* reduces glass particulate generation while enhancing machinability.

With so much riding on the quality and availability of your product, isn't it time to consider a more reliable option?

Visit **www.corning.com/valorpda** to learn how Corning's advanced Valor Glass technology protects 21st century medicines essential to patient care.

*Compared to conventional borosilicate

March 2019 PDA Letter

Industry Eyes Future of Visual Inspection

Five Critical Areas of Concern Draw Attention of Pharma Industry

John Shabushnig, PhD, Insight Pharma Consulting; Markus Lankers, PhD, MIBIC; John Ayres, MD, Pharma Safety Solutions; Roy Cherris, Bridge Associates; Robert Miller, Pfizer; Romain Veillon, GSK Vaccines; and Rick Watson, Merck

It goes without saying that visual inspection is critical to parenteral manufacturing. All units produced must be inspected to ensure a high level of quality assurance. Visual inspection can be performed with the human eye by a trained inspector under controlled conditions or via automation using advanced camera and computer technology.

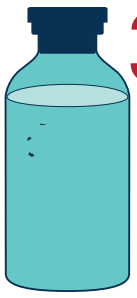
Cover photo courtesy of Antares Vision. This photo depicts the company's Visual Rotating Inspector machine

The Challenges of Visually Inspecting IV Bags

Florian Krickl, Vitronic

Is there a common technical standard for automated visual inspection in difficult-to-inspect parenteral products? Talk with any quality manager or project engineer in the pharma manufacturing sector and they will tell you that there are a number of processes where inspection results often do not meet the expectations. As long as there is no independent standard defining the quality of automated visual inspection, however, inspection results can vary significantly case by case. This is a particular concern for IV bags.

InfoGraphic



Can We Achieve "0" Defects for Visible Particles?

Find out what can be done to accomplish this challenging goal in the latest *PDA Letter* InfoGraphic!

Big Data is Here to Stay

2018 PDA Manufacturing Intelligence Workshop Commands a Crowd

Aaron Goerke, PhD, F. Hoffmann-La Roche AG, and Michele D'Alessandro, Merck & Company, Inc.

Implementing big data within pharmaceutical manufacturing will require extensive collaboration. Fortunately, a 2018 PDA workshop suggests this is possible.

PDA Letter

Volume LV • Issue 3 www.pda.org/pdaletter

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

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

Subscriptions are not available.

Departments

Digital Exclusives

> **On the Issue** | P. Acnes in an Aerobic Process
Merck's **Kenneth Boone** covers recovery of anaerobic microorganisms from an aerobic aseptic process simulation.

> Change is in the Air for Packaging Components
West's **Cathy Zhao** offers her perspective on the latest packaging trends.

pda.org/letter

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

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

PDA TRAINING & RESEARCH INSTITUTE
4350 East West Hwy., Suite 150
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (240) 482-1659
info-tri@pda.org

Game Changer

Going to Interphex?
Visit us at booth 1827

Educational Session:
Hidden Problems with Relaundering Microfiber Mops
on April 3 at 11:30 am

At Contec, we don't just make cleanroom products – we've transformed the cleanroom industry. We don't just follow best practices, we created them. So know that when you clean with Contec, you're not just cleaning – you're putting up the industry's strongest defense against contaminants.

CONTEC® | WHATEVER IT TAKES™

PDA Keeps You up to Date on the Latest Advances in Packaging Science

PDA Parenteral Drug Association

Medical and technological advances are revolutionizing patient treatment options, creating new challenges and opportunities for the parenteral packaging market.

PDA is a recognized leader with longstanding expertise and focus in packaging science. In light of new developments and the dramatic impact of primary packaging on the safety and efficacy of drug product, PDA is intensifying its efforts to provide the most up-to-date tools and resources to the industry.

A snapshot of PDA's extensive offerings includes:

- **Global Conferences and Workshops** on topics such as glass quality, parenteral packaging, container closure integrity testing, and pre-filled syringes
- A broad array of **Topic-specific Training Courses**
- **Technical Reports and Resources,** both already published and under development
- **Interest Groups** dedicated to addressing pharmaceutical packaging issues
- **The Ed Smith Packaging Science Award,** granted annually to recognize outstanding contributions to PDA and Pharmaceutical Packaging Science

CONNECTING PEOPLE SCIENCE AND REGULATION®

To find out more about how PDA is leading the way to improved patient safety through better pharmaceutical packaging processes and practices, please visit pda.org.

Visual Inspection Technology: Not Just for the Pharma Industry

Rebecca Stauffer @RebeccaStauPDA

I am looking forward to the *Visual Inspection Forum* in April! This is one of my favorite PDA meetings, and I really enjoy the opportunity to learn about new advancements in visual inspection technology. For example, visual inspection is becoming increasingly automated like other aspects of parenteral manufacturing ***(1).*** At the same time, other industries are also adopting innovative technological approaches to visual inspection.

Food packaging is one such industry. None of us want to purchase flour in packages prone to leaking and end up with a car interior that resembles Antarctica. Manufacturers of food and beverage cartons are looking at in-line visual inspection systems that identify problems quickly without reducing in-line speeds ***(2).***

In the aerospace sector, remote visual inspection is an option ***(3).*** This technology uses video borescopes to allow aerospace equipment manufacturers to inspect for corrosion, leaks, surface cracks and the like. In many ways, these aerospace engineers are like doctors interpreting endoscopy or MRI results. Remote visual inspection enables more efficient inspections in real-time for this sector ***(3).***

Inspectors in the nuclear industry are using panoramic photo techniques to help them complete visual inspection activities more efficiently ***(4).*** Who would have thought that a function we sometimes use to take sweeping pictures on our smartphones could help ensure safety at nuclear energy sites?

Clearly, advancements in visual inspection technology do not benefit parenteral manufacturers alone, they support the capabilities of a breadth of global industries. Pharma, I am sure, can learn how these other industries are handling advancements in visual inspection. One way to expand your knowledge in this area is to attend the *2019 PDA Visual Inspection Forum* in Washington, D.C. For the first time ever, this popular PDA meeting will be held in the spring. There may even be a few cherry blossoms still blooming, provided the polar vortex did not impact them.

References

1. Prinz, H. "Automated Visual Particle Inspection." Pharmaceutical Technology 41 (Oct. 2, 2017) 68–74. http://www.pharmtech.com/automated-visual-particle-inspection
2. "Tech Advances in Package Manufacturing – Visual Inspection Systems Spotlight." Esource News. Valco Melton (Dec. 18, 2018) https://blog.valcomelton.com/tech-advances-package-manufacturing-visual-inspection-systems-spotlight/
3. Laffont, T. "Turbine Technology: Advances in Remote Visual Inspection." AviationPros.com (Sept. 5, 2014) https://www.aviationpros.com/tools-equipment/inspection-testing/article/10225661/turbine-technology-advances-in-remote-visual-inspection
4. Wood, D. "Taking Visual Inspection Technology to a New Level." Power (March 1, 2018) https://www.powermag.com/taking-visual-inspection-technology-to-a-new-level/

PDA Welcomes Ruth Miller

In November, **Ruth Miller** joined the PDA family as the new Director of Regulatory Affairs in the Scientific and Regulatory Affairs department. In this role, she supports PDA's regulatory communications and manages the activities of the Regulatory Affairs and Quality Advisory Board.

Previously, Ruth was Senior Director of Regulatory Affairs with the Healthcare Distribution Alliance. She has also worked for the U.S. Pharmacopeia and the law firm Covington & Burling. She earned her law degree from the Boston University School of Law and her bachelor's degree from the College of William and Mary.

Ruth fills the position previously occupied by **Denyse Baker** who is now Senior Policy Director, U.S. Regulatory Affairs, at AstraZeneca.

Board of Directors Nominations Needed

The PDA Nominating Committee is seeking recommendations from members for candidates to fill Officer (Chair-Elect, Treasurer and Secretary) and Board of Director positions for terms beginning in 2020. Nominees must be current PDA members in good standing. Recommendations will be considered and evaluated by the PDA Nominating Committee. This year's committee is chaired by Immediate Past Board of Director's Chair **Martin VanTrieste** and includes current Board of Director's Chair **Rebecca Devine** and Board of Director's Chair-Elect **Jette Christensen.**

If you are interested in being considered or want to recommend a colleague, send the recommendation via email to nominate@pda.org or mail to PDA Global Headquarters, Bethesda Towers, Suite 600, 4350 East West Highway, Bethesda, MD 20814, USA, attention: President. In addition to your recommendation, please include any other supporting information that may make it easier for the Nominating Committee to evaluate your recommendation.

Nominations are due April 26.

If you have any questions or feedback about the nominating process, please feel free to contact PDA President **Richard Johnson** at johnson@pda.org.

PDA Opens Asia Pacific HQ

On Feb. 21, PDA announced the launch of PDA Asia Pacific, headquartered in Singapore, the Association's second office outside North America.

The move will better serve a growing membership throughout Asia and thriving chapters in Japan, Australia, Singapore, South Korea and Taiwan. With a permanent presence in Southeast Asia, PDA will increase the number of conferences and professional training offered to pharmaceutical professionals throughout the region, and expects to see membership there grow as well.

"PDA is proud to announce the establishment of PDA Asia Pacific," said **Richard Johnson,** PDA President & CEO. "Our team will help PDA expand our activities in this important region and support our members and chapters there. This will be a parallel organization to PDA Europe and PDA North America, and together with PDA's Global Headquarters, will help us Connect People, Science and Regulation® across our community."

PDA Volunteer Spotlight

Kim Sobien

- **Principal Sterility Assurance Engineer**
- ***PETNET Solutions***
- Member Since | **2001**
- Current City | **Wake Forest, North Carolina**

Gathering new perspectives is crucial to helping the industry move forward

Describe your volunteer experience on the program planning committee for *PDA's Global Conference on Pharmaceutical Microbiology*.
I have truly enjoyed participating on the committee behind this seminal conference over the years. The committee is always full of inspiring colleagues with diverse backgrounds and vast knowledge.

Each person on the committee has introduced me to new ways of thinking. It is fun to collaborate with like-minded volunteers eager to work together to deliver a fresh and timely program year after year. I feel that this experience has helped me get out of my comfort zone and made me more confident.

Do you have any advice for new volunteers?
Come join us! Please do not hesitate to contact someone at PDA; we would be happy to help you get started. There are so many opportunities to volunteer with PDA—committees, task forces, technical report teams, conference speakers, just to name a few. Gathering new perspectives is crucial to helping the industry move forward. All levels of experience and expertise are welcome!

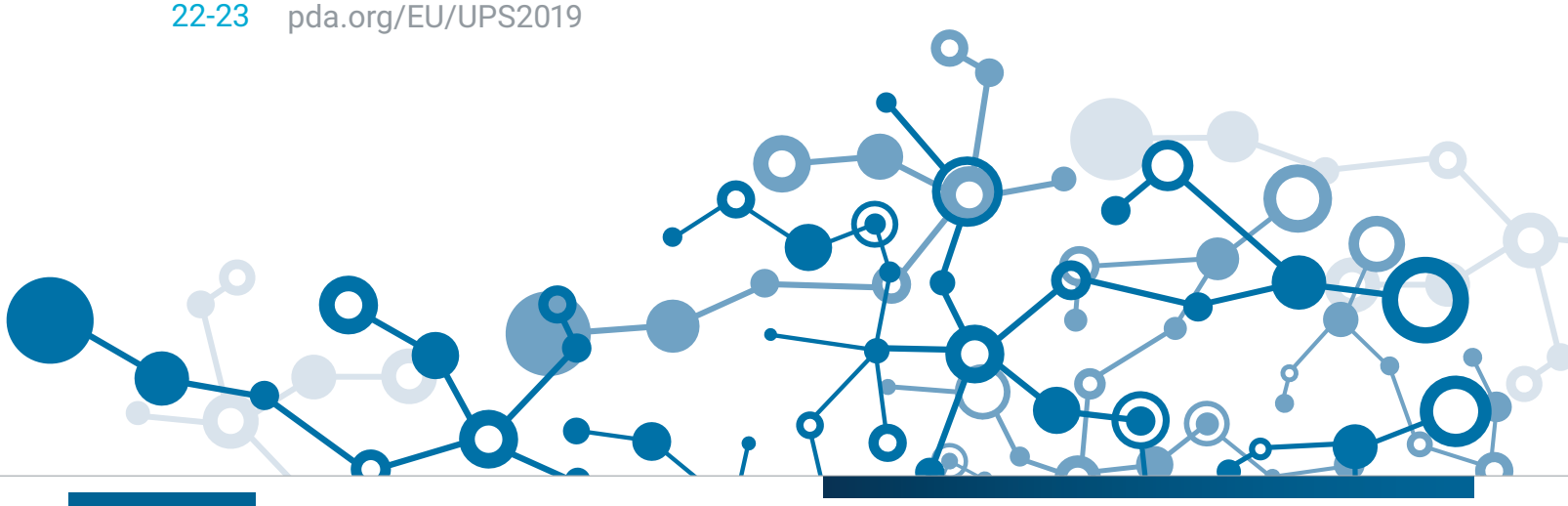
What lessons have shaped your work life?
The only constant is change. If you can become skilled at managing change, big transformations can be well controlled, highly valuable, and, ultimately, even enjoyable. Also, do not forget to normalize your data. These lessons are applicable both inside and outside of work.

Who inspired your current career path?
I had amazing, caring and involved professors in my undergraduate microbiology program at the University of Wisconsin-La Crosse. They not only set high academic standards for us, but they let us have a lot of fun while becoming microbiologists. Most importantly, they occasionally even let us experience failure, which taught us even more.

Who is your personal hero?
I am a huge admirer of **Anthony Bourdain.** He never shied away from openly sharing his passion for travel, food and, especially, people. He showed us the fascinating and real parts of cultures that we might not know about otherwise. Bourdain owned his confidence and enthusiasm and that is an inspiration to me.

REGISTER NOW
for PDA's 2019 Signature Events

MARCH 11-13	***2019 PDA Annual Meeting*** pda.org/2019Annual	San Diego, CA
MARCH 19-20	***2019 PDA Europe Parenteral Packaging Conference*** pda.org/EU/ParPack2019	Venice, Italy
APRIL 23-24	***2019 PDA Visual Inspection Forum*** pda.org/2019Visual	Washington, DC
MAY 16-17	***2019 PDA Europe Pharmacopoeia Conference*** pda.org/EU/Pharma2019	Geneva, Switzerland
JUNE 25-26	***4th PDA Europe Annual Meeting*** pda.org/EU/Annual2019	Amsterdam, The Netherlands
SEPTEMBER 3-4	***2019 PDA Europe BioManufacturing Conference*** pda.org/EU/Bio2019	Munich, Germany
OCTOBER 21-23	***14th Annual PDA Global Conference on Pharmaceutical Microbiology*** pda.org/2019Micro	Rockville, MD
OCTOBER 22-23	***2019 PDA Universe of Pre-Filled Syringes and Injection Devices*** pda.org/EU/UPS2019	Gothenburg, Sweden



CONNECTING PEOPLE SCIENCE AND REGULATION®

To see the complete list of PDA's 2019 events, visit pda.org/Conferences

Student Chapter Gains Stem Cell Insights

Kathryn MacDonald, Middlesex Community College

It is not every day that college students have the opportunity to learn firsthand about stem cell advancements directly from a leading expert in the field. Last fall, the PDA New England Chapter's student chapter provided just such an opportunity for fellow students at Middlesex Community College.

On Oct. 12, the chapter hosted **Dr. Laurence Daheron**, one the nation's leading stem cell researchers and head of the Harvard Stem Cell Institute. On the day of the event, those involved in planning worked in a flurry of nervous energy. Student chapter president **Zeel Patel** had her hands full coordinating event setup while also driving to Cambridge, Mass. to pick up Dr. Daheron. This left the rest of the setup to president-elect **Katie McManus** and it proved a real team effort—as a group, there was a sense that this was a make or break situation. After weeks of blanketing the campus with posters and promoting the event via social media, all the student chapter volunteers wondered how many students would actually be interested enough to spend a Friday night learning about stem cells.

Quite a number as it turned out! Turnout proved impressive. Not only were biotechnician students in attendance but even early childhood education majors and undecided students joined the crowd! Both college and chapter leaders were in attendance as well, including College President **James Mabry,** Advisor **David Kalivas** and **John Masiello** from the PDA New England Chapter.

Dr. Daheron began her presentation by covering the basics of stem cells and their potential. She explained all the potential stem cells have in treating a plethora of ailments. Stem cells have the ability to turn into any cell in the body but, once they specify, they cannot go back…that is, until scientists learned how to reset them.

Currently, the two main applications for stem cells are cell therapy and disease modeling. Cell therapy involves fixing mutated genes, growing them in vitro and then transplanting them back into the patient. Disease modeling involves in vitro differentiation, testing to find drugs that prevent a disease (for example, motor neurons) and then creating a drug to prevent the death of the targeted cell. This process is more affordable and can treat more than one patient at a time, whereas cell therapy is costlier and only administered to an individual patient.

Dr. Daheron then covered how samples are taken from a person's blood, skin or urine, because these samples are easily attained and the procedure noninvasive. She also explained in depth the Sendai virus and how scientists are trying to reprogram the virus. Working with this virus required several layers of safety as they are testing the surface of what reprograming can do. This virus is nonpathogenic to humans and does not go through a DNA phase, meaning it will not integrate into the host's genome. She then explained how the Institute's reprogramming kit, CytoTune2®, works and its application to the Sendai virus.

Dr. Daheron went on to talk about gene editing. While studying pluripotent stem cells, scientists will knock out certain genes to see what their functions are and cut in mutations to healthy donor lines to get a control. She explained how she uses CRISPR/CRISPR-associated genes to cut out specific sequences of the DNA.

Moving on to disease modeling, Dr. Daheron mentioned that the two main primary patient cells are transgenic animals and immortalized cell lines (such as HeLa cells). Monogenic diseases, such as amyotrophic lateral sclerosis (ALS), muscular dystrophy and cystic fibrosis, are easier to study, and have the potential to be repaired using CRISPR technology.

Dr. Daheron moved on to a specific disease her lab is working on—ALS. She gave a quick epidemiology summary for the disease. She mentioned there were over forty genes involved in the mutation and that, since 1995, only two medications have been approved to help treat ALS. She concluded her presentation with an overview of her research on ALS genetic mutations.

All stem cell research is fairly new. Over the past 12 years, the technology has rapidly progressed. Dr. Daheron is an amazing scientist working on a game-changing gene mutation treatment and the New England student chapter was honored to learn about her work.

The chapter thanks everyone involved in making this event possible.

PDA Who's Who

Laurence Daheron, PhD, Head, iPS Core Facility, Harvard University

David Kalivas, PhD, Faculty and Advisor, Middlesex Community College

James Mabry, PhD, President, Middlesex Community College

John Masiello, Executive Vice President, Masy BioServices

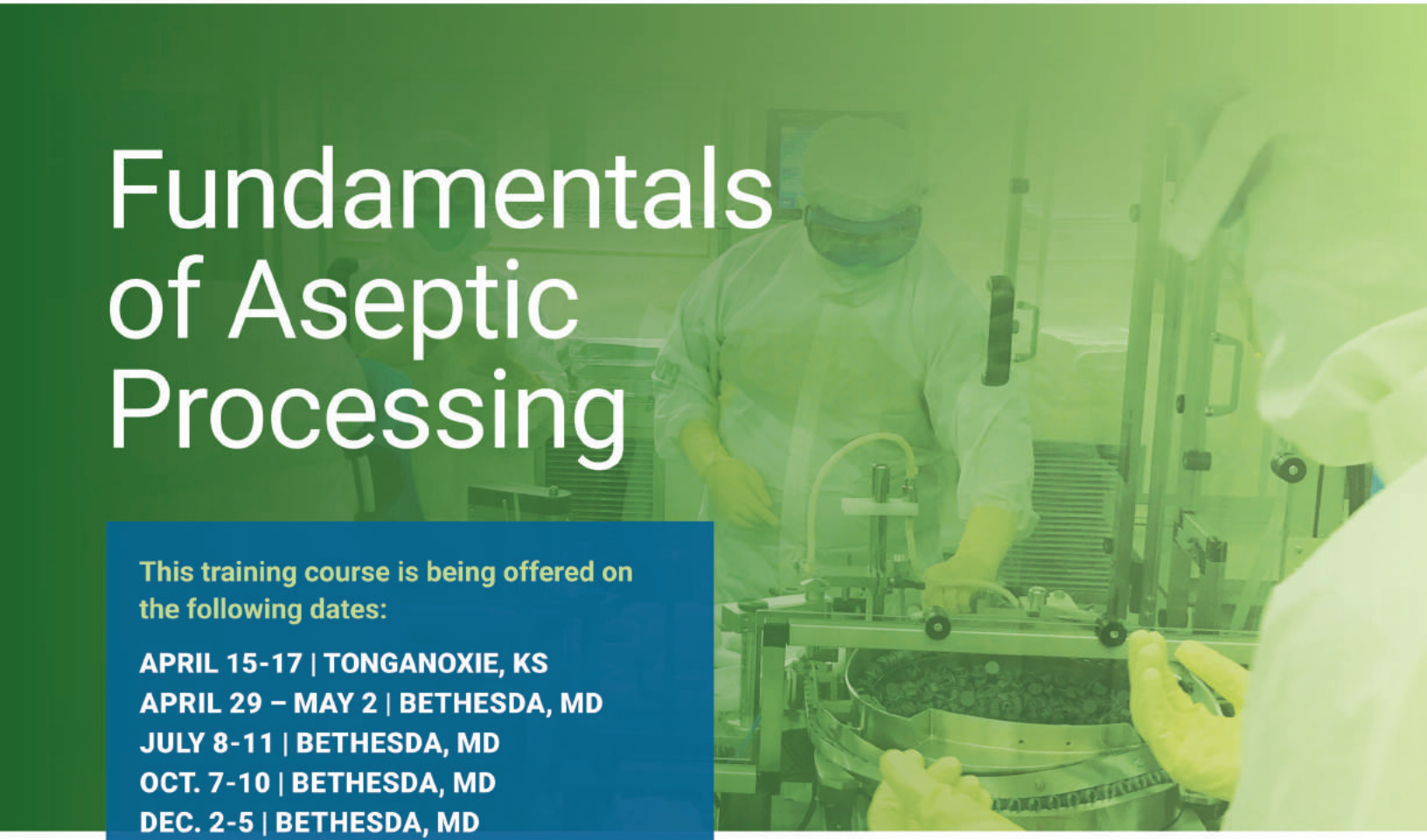
Katie McManus, Student, Middlesex Community College

Zeel Patel, Student, Northeastern University

PDA
Parenteral Drug Association

pda.org/FundamentalsAP

Fundamentals of Aseptic Processing



This training course is being offered on the following dates:

APRIL 15-17 | TONGANOXIE, KS
APRIL 29 – MAY 2 | BETHESDA, MD
JULY 8-11 | BETHESDA, MD
OCT. 7-10 | BETHESDA, MD
DEC. 2-5 | BETHESDA, MD

Gain an understanding of the principles, processes, and systems related to aseptic operations with this interactive training course.

Improve job performance through newly acquired practical knowledge and skills.

Topics to be addressed include:

- Facility/Equipment/ Process Design
- Environmental Monitoring
- Airflow Studies
- Aseptic Gowning
- Disinfectant Efficacy
- Sanitization Techniques
- Filtration Processes
- Moist Heat Sterilization
- Aseptic Process Simulations (Media Fills)
- Reading and Evaluating Microbial Results
- Visual Inspection

CONNECTING PEOPLE SCIENCE AND REGULATION®

PDA is an accredited provider of continuing education, offering high-quality, relevant training for both new and experienced professionals working in industry, government (health authority), and academia. Visit *pda.org/courses* for more information.

SNAPShot

New Datwyler Site Showcases Flexible Manufacturing

Jahanvi (Janie) Miller, PDA

Innovation in the pharma industry comes in the form of new drug products and novel manufacturing/production techniques. Both must be held to the highest standards of safety and quality. Various innovations are leading to facilities designed to meet these high standards.

In late September, I had the opportunity to attend the grand opening of packaging supplier Datwyler's facility in Middletown, Del. The design of this facility mirrors that of their sites in Belgium and India and showcases the company's philosophy of reducing risk to products through innovative design.

Datwyler manufactures components for drug packaging at this facility using their "First Line" manufacturing processes. Intended to achieve zero defects relating to their products, this facility minimizes potential risks from human error **[Editor's Note:** For more on "zero" defects, see the infographic on page 32**].** The plant was configured with future needs and changing environments in mind. Their fluoropolymer spray-coating technology reduces the chance of defects from silicone particulates and automated technologies reduce operator interventions. The lean design of the facility allows full visibility of all manufacturing processes from walk-through corridors, giving visitors the opportunity to view all aspects of production.

I truly enjoyed seeing this new design in operation. As PDA strives to identify best practices in manufacturing science, we look forward to new technologies that achieve higher levels of patient safety. I can tell you from my experience that manufacturers and suppliers are rising to the challenge of anticipating new technologies and meeting the requirements set forth by regulators.

Journal *TOC*

Read the Latest Aseptic Processing Research in the March/April PDA Journal

How can continuous environmental monitoring reduce interventions during aseptic manufacturing? Find out in the latest issue of the *PDA Journal of Pharmaceutical Science and Technology* (journal.pda.org).

Research

Jakob Buecheler, et al., "Residual Seal Force (RSF) Testing: A Suitable Method for Seal Quality Determination also for High Potent Parenterals"

Jeffrey Weber, et al., "Continuous Microbiological Environmental Monitoring for Process Understanding and Reduced Interventions in Aseptic Manufacturing"

Dennis Jenke, "Application of Arrhenius Kinetics to Acceleration of Controlled Extraction Studies "

Tech/App

Søren Dahl, et al., "Container Closure Integrity Testing – Method Development for Freeze Dryed Products Using laser based Headspace Oxygen Analysi"

Commentary

Dennis Jenke, "How One Might Experimentally Determine if Container Closure Systems and their Components and Materials of Construction Contribute Elemental Impurities to Packaged Pharmaceutical Drug Products"

Paul Barone, et al., "Biopharmaceutical Industry Approaches to Facility Segregation for Viral Safety: An Effort from the Consortium on Adventitious Agent Contamination in Biomanufacturing"

Review

Joseph N. Tanyous, "Cleaning Validation: Complete guide for health-based approach in chemical cross contamination risk assessment "

IMPROVING PATIENTS' LIVES THROUGH OUR INNOVATIVE HEALTHCARE SOLUTIONS IS THE CORE OF OUR BUSINESS. **BECAUSE WE CARE.**

Datwyler's most advanced manufacturing standard, First Line, is specially designed to manufacture pharmaceutical rubber components for high-end pharmaceutical and biotech markets in a fully integrated cleanroom environment conforming to the highest industry standards. All facilities aligned with the First Line manufacturing standard are specially designed and operated under a zero-defect philosophy.

www.sealing.datwyler.com

DATWYLER

Viruses on the Surface

Assessment of Viral Inactivation of Cleaned Surfaces Using a Chlorinated Alkaline Solution

Jennifer Loughman and Paul Lopolito, STERIS

Viral safety from endogenous and adventitious viruses remains a concern within biopharmaceutical manufacturing. The risk-based approach described by regulatory agencies incorporates three principles: selecting raw materials for the absence of viruses and animal-derived components; testing at various stages of production to ensure absence of viruses and assessing the capability of the process to inactivate viruses ***(1–3)***.

Equipment, tanks and transfer lines are often cleaned with an automated clean-in-place (CIP) system, while small parts are often cleaned manually or via an automated clean-out-of-place (COP) parts washer. Automated cleaning systems allow for safe use of alkaline cleaning solutions at high concentrations and high temperatures to ensure viral inactivation ***(4).*** Unfortunately, the higher concentrations and temperatures impose a safety risk for manual cleaning or open COP operations.

A 2010 study investigated viral inactivation with a sodium hydroxide and potassium hydroxide-based alkaline cleaning solution at ambient temperature and 45 °C using both enveloped and nonenveloped viruses dried onto stainless steel surfaces ***(5).*** An additional study along similar lines was presented as a poster at *Interphex* last year and summarized in this article. The purpose of the research is to evaluate viral inactivation using a chlorine containing alkaline cleaning solution at ambient temperature and 45 °C against porcine parvovirus (PPV) and bovine viral diarrhea virus (BVDV) at 45 °C. These viruses were selected because they represent highly resistant enveloped and nonenveloped viruses.

Measures to Test for Viruses

The materials consisted of a BVDV strain (NADL, American BioResearch Lab with host cell line MDBK, ATCC CCL-22) and a PPV strain (NADL-2, ATCC VR-742 with host cell line ST, ATCC CRL-1746). **Figure 1** illustrates the process.

The test method followed the procedures of ASTM E1053-11, modified to use a 304 stainless steel carrier (1 cm diameter), with interfering conditions based on EN 14476:2013 ***(6).*** The dirty condition included a final concentration in the reaction mixture of 3 g/L bovine serum albumin (BSA) and 3 mL/L sheep erythrocyte solution. The clean condition did not contain any BSA or blood.

Dilutions of a chlorinated alkaline test solution were prepared in hard water at (v/v) concentrations of 0.65%, 0.90% and 1.30%. The contaminated carriers were treated with 50 µL of test product dilution and held for the required contact times of 2, 5, 10 and 30 minutes. Treatment conditions consisted of ambient temperature (20 °C) or elevated temperature (45 °C); test product was preheated to 45 °C and the treated carriers were held in an incubator at 45 °C for duration of contact time. After the contact time, carriers were neutralized with 950 µL of neutralizer, and carriers were scraped and vortexed for 60 seconds to recover virus. A recovery control, where contaminated carriers were treated with media only at ambient temperature for the longest contact time, was used to determine the baseline amount of infectious virus. Additional controls for neutralizer effectiveness, cytotoxicity, cell viability and virus stock titer were also performed.

Residual infectious virus in test and control samples was detected by viral-induced cytopathic effect (CPE). Dilutions of test and control samples were added to cultured host cells and incubated at 36 °C with 5% CO_2 for a time appropriate for each challenge virus. Cultures were examined microscopically and scored for infectious virions, virus-specific CPE and test substance-specific cytotoxic effects. Samples were analyzed in singles.

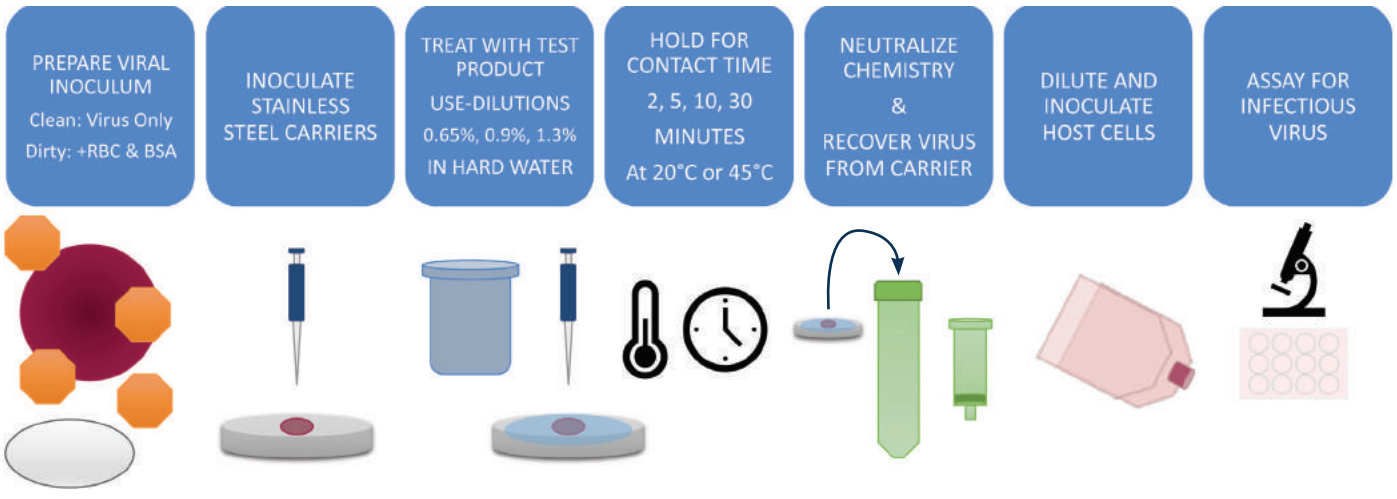


Figure 1 Diagram of Virucidal Hard Surface Efficacy Test Procedures

PPV inactivation was impacted by contact time and interfering conditions

The 50% tissue culture infective dose per mL ($TCID_{50}$) was calculated for each sample and log_{10} transformed. For samples containing no detectable virus, the limit of detection for the assay determined the theoretical maximum titer. The log reduction was calculated by subtracting the output viral load (log_{10} $TCID_{50}$) from the input viral load (log_{10} $TCID_{50}$).

Elevated and Ambient Temp Results

For elevated temperatures, complete inactivation of both PPV and BVDV was observed at product concentration as low as 0.65%, and the log reduction was determined based on the assay limit of detection, as shown in **Table 1**.

To investigate viral inactivation with a less stringent process, testing was performed at ambient temperature (20 °C) under "clean" and "dirty" conditions **(Table 2).**

As shown in **Table 2,** there was a dose-dependent reduction of the challenge virus. PPV inactivation was impacted by contact time and interfering conditions, with ≥3 log reduction observed after treatment with a 1.3% solution for 10 minutes (clean) or 30 minutes (dirty).

Conclusion

Viral inactivation testing with a chlorinated alkaline test solution achieved greater than 3.5 log reduction of PPV and greater than 4.1 log reduction of BVDV using a minimal exposure condition of five minutes at 0.65% v/v and 45 °C. While intriguing, further study is needed to ascertain the use of a chlorinated alkaline test solution for viral inactivation.

[Editor's Note: Coauthor **Paul Lopolito** will present a podium presentation on this topic at *Interphex* in April**].**

Table 1 Viral Inactivation of PPV and BVDV at 45 °C, Clean Conditions (n.d.=not determined)

Time (min)	Log Reduction PPV, clean conditions			Log Reduction BVDV, clean conditions		
	0.65%	0.9%	1.3%	0.65%	0.9%	1.3%
2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
5	≥3.50	≥3.50	≥3.50	≥4.10	≥4.10	≥4.10
10	≥3.50	≥3.50	≥3.50	≥4.10	≥4.10	≥4.10
30	≥3.50	≥3.50	≥3.50	≥4.10	≥4.10	≥4.10

Table 2 Viral Inactivation of PPV at Ambient Temperature (20 °C), Clean and Dirty Conditions

Time (min)	Log Reduction PPV, clean conditions			Log Reduction PPV dirty conditions		
	0.65%	0.9%	1.3%	0.65%	0.9%	1.3%
2	0.63	1.25	2.38	0.63	1.88	1.38
5	0.63	1.88	2.88	0.75	1.75	1.38
10	1.75	1.75	3.88	1.00	1.88	1.88
30	1.63	1.75	3.63	1.63	1.63	3.00

References

1. ICH Harmonized Tripartite Guideline Q5A(R1)
2. EMA, Guideline on viral safety evaluation of biotechnological investigational medicinal products
3. Stokes, A. Managing potential virus and TSE contamination: a risk-based approach for cGMP biopharma manufacturing facilities. *Pharm. Eng* (March/April 2018): 63-67.
4. Borovec, S., et al. (1998) Inactivation Kinetics of Model and Relevant Blood-borne Viruses by Treatment with Sodium Hydroxide and Heat. *Biologicals* 26 (1998):237-244.
5. Eterpi, M., McDonnell, G., and Thomas, V. "Virucidal Activity of Disinfectants Against Parvoviruses and Reference Viruses" *Applied Biosafety* 15 (2010)):165-171.
6. Research conducted at STERIS Corporation.

About the Authors

Jennifer Loughman, PhD, is a senior scientist in the Research and Development Microbiology Laboratory at STERIS Corporation. She has over 20 years of academic and industrial microbiology experience.

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

Published online first

Biopharma Offers New Opportunities

Cristiana Campa, GSK, and Michael De Felippis, PhD, Eli Lilly and Company

Biopharmaceutical products have become increasingly important medicinal tools within the past 40 years. The ability of these products to address previously untreatable diseases, coupled with their favorable safety and efficacy profiles, has driven consumer demand. The market for biopharmaceuticals was valued at U.S. $218 million in 2017, with continued growth projected over the next decades. Further research into these products has led to improved manufacturing processes and enhanced product quality. Thanks to these improvements, sufficient quantities of highly purified biopharmaceuticals have reached the global supply chain. Regulators have also kept pace with these developments by establishing guidelines to ensure access to these innovative treatments.

PDA has played an essential role in advancing the field of biopharmaceuticals as well by arranging conferences, workshops and training courses covering general areas of manufacturing technology, quality control and regulation of biopharmaceutical products. Meetings have focused on vaccines, monoclonal antibodies and related technical disciplines, such as pharmaceutical microbiological control, expanding opportunities for dialogue among academia, industry and regulators. These are just a few examples of how PDA has helped to define best practices and promote the sharing of knowledge in the biopharmaceutical field.

Recognizing the critical role that pharmaceutical manufacturing will continue to play in enabling future biopharmaceutical innovation, PDA Europe is introducing a new conference series spotlighting the science and technology of biopharmaceutical manufacturing. The inaugural *BioManufacturing* conference will be held in Germany in September 2019. This event will provide a forum for communicating innovative approaches and discussing current and emerging topics related to process, product and analytics, with particular emphasis on vaccines and therapeutic proteins. By combining several topic-specific conferences into a single meeting of broader scope, PDA wants to emphasize the important synergies connecting various product platforms and create opportunities to share knowledge across multiple disciplines.

The *BioManufacturing* conference will feature both presentations and panel discussions as well as meetings of PDA interest groups connected with biopharmaceutical manufacturing. Representatives from industry, academia and regulatory agencies are invited to attend this event and to consider presenting on the program.

BioManufacturing Conference
Sept. 3–4
Munich
www.pda.org/eu/bio2019

Published online first

Can the Power of Viruses be Harnessed for Good?

Brian Hawkins, PhD, Pluristyx, Inc.

Viruses are ubiquitous agents that can infect all forms of life and result in genome alterations that kidnap host cells and outwit immune defenses.

Medical advances, however, have enabled researchers to harness the unique qualities of viral genome editing, resulting in genetically modified cells that can synthesize biopharmaceuticals or even act as "living drugs" to attack and eradicate chronic diseases such as cancer.

2019 PDA Virus Safety Forum

May 8

Long Beach, Calif.

www.pda.org/2019biopharmweek

As biopharmaceuticals continue to advance, what role will viruses play in the production of innovative therapies? And as researchers use viruses to produce living drugs, how can patient safety be assured?

PDA will host the *2019 PDA Virus Safety Forum.* This one-day event begins with a breakfast session highlighting the work of PDA's Advanced Virus Detection Interest Group and extended discussion on current advances in viral testing, mitigation and clearance. A panel discussion will focus on the practical application of viral safety protocols in biopharmaceutical manufacturing.

Following the breakfast session, plenary sessions will feature expert talks on a comprehensive virus safety strategy that includes testing, mitigation and clearance of adventitious viral agents. Commonly referred to as the "safety tripod," testing, mitigation and clearance will be addressed as part of a risk-based approach to viral safety, with presentations addressing the use of qualified raw materials, the detection of both known and unknown viral agents, incorporation of viral manufacturing controls, the relative merits of conventional assay and methods to inactivate or remove viral particles from finished product. Incorporation of these manufacturing controls can dramatically reduce the negative impact of adventitious viral particles and provide a robust platform to improve the safety of biopharmaceutical products.

Industry Eyes Future of Visual Inspection

Five Critical Areas of Concern Draw Attention of Pharma Industry

John Shabushnig, PhD, Insight Pharma Consulting; Markus Lankers, PhD, MIBIC; John Ayres, MD, Pharma Safety Solutions; Roy Cherris, Bridge Associates; Robert Miller, Pfizer; Romain Veillon, GSK Vaccines; and Rick Watson, Merck

Article at a Glance

- U.S. and EU pharmacopeias seek to harmonize visual inspection chapters
- Technological advancements in automation inspection continue
- Lifecycle approach needed for difficult-to-inspect parenterals

> **The 100% visual inspection standard has been established by design and is required by global pharmacopeias**

It goes without saying that visual inspection is critical to parenteral manufacturing. All units produced must be inspected to ensure a high level of quality assurance. Visual inspection can be performed with the human eye by a trained inspector under controlled conditions or via automation using advanced camera and computer technology.

Because visual inspection is a vital function of any manufacturing process, keeping current with advancements in technology and global regulations is crucial. The following five topics, in particular, require additional discussion: regulatory and compendial changes, automation, difficult-to-inspect products, inspection control and monitoring strategies and updated requirements for container closure integrity testing.

Recent Regulatory and Compendial Changes

A review of data found on the U.S. FDA website shows continuing recalls associated with visible particles in injectable drug products. While the number of such recalls peaked in 2014, they continue to occur. The variety of particle types and companies involved suggest multiple root causes, which means no single corrective action is enough. Robust visual inspection processes are required to provide critical information to drive continuous process improvement and guard against significant process deviations.

Guidance on inspection methods and requirements can be found in global pharmacopeias. The United States Pharmacopeia (USP) published General Chapter <790> Visible Particulates in Injections covering inspection conditions and acceptance criteria in 2014, followed by <1790> Visual Inspection of Injections in 2017. Here, inspection conditions were harmonized with the European Pharmacopoeia (Ph. Eur.). Acceptance criteria based on widely used acceptance sampling plans were also established and Ph. Eur. published an update to its Chapter 2.9.20 Particulate Contamination: Visible Particles in 2018 which will become effective in 2019. In 2018, Ph. Eur. also published a draft of a new "non-mandatory" Chapter 5.17.2 Recommendations on Testing of Particulate Contamination: Visible Particles. This chapter, when finalized, will provide further guidance on complying with EU inspection requirements.

Beyond USP and Ph. Eur., the Japanese Pharmacopoeia (JP) updated their Chapter 6.06 Foreign Insoluble Matter in 2016 to harmonize inspection conditions with the USP and Ph. Eur. All these actions have brought global expectations for visual inspection closer together; however, differences—especially in acceptance criteria—continue to exist.

In 2017, the European Commission published a draft revision to Annex 1 Manufacture of Sterile Medicinal Products of the EU GMP guidelines. This covered many important topics including environmental monitoring, filtration and sterilization, as well as the finishing of sterile products. This latter section expanded the requirements for visual inspection, including prohibiting use of visual inspection to ensure container integrity for all container types. Further expectations were established on inspector qualification, alternative method qualification, use of defect libraries and trending of inspection results. An update regarding implementation and/or a revised draft is anticipated in 2019.

Automated Inspection

Automated visual inspection has been constantly evolving since its emergence in the pharmaceutical industry four decades ago. Advances in sensor technology and new artificial intelligence (AI) algorithms, such as deep learning, are likely to reshape visual inspection. Since the introduction of automated visual inspection with charged coupled device cameras and linear array sensors in the late 1970s, industrial PCs and image processing algorithms in 1980s, faster processing and machine capacities in the 1990s and compact and robust LED lighting in 2000s, many innovations have greatly enhanced the capability of automated inspection machines.

Improved illumination is a critical element for advancements in automated visual inspection. Last year saw development of multispectral lighting and structured color lighting methods that offer improved specificity, better discriminating true defects from artifacts such as air bubbles—a common cause of false rejects. Spectral illumination beyond the visible range, such as in the near-infrared region, can support the inspection of difficult-to-inspect products such as lyophilized cakes. ➤

All these topics and more will be discussed at the *2019 PDA Visual Inspection Forum,* April 23–24 in Washington, D.C. To learn more and to register, visit: www.pda.org/2019visual.

> **When batches exhibit abnormal defect rates, an investigation should be initiated**

Recent advances in image processing algorithms can now analyze particle trajectories inside parenteral containers, again with the goal of differentiating true contaminating particles from air bubbles.

Deep learning's emergence is likely to reshape automated visual inspection. The potential of deep learning was first established in 2012 using an Alexnet neural network that achieved previously unmet accuracy in image classification. Proof of concept for deep learning was presented at the 2018 *Visual Inspection Forum* in Berlin, showing that complex parenteral defects, such as cracks and particles, were readily detected (detection rates > 99%) and correctly classified (false reject rate < 1%) with this approach.

Deep learning also brings with it several questions:

- How do we validate these inference models?
- Will human inspection remain the reference method for visual inspection?
- What will regulators require to gain confidence in these models?
- Will we move from supervised to unsupervised learning algorithms?

Answering these requires close cooperation among machine builders, industry users and regulators. PDA is a unique organization that can help drive this change.

Difficult-to-Inspect Products

The 100% visual inspection standard has been established by design and recognized by global pharmacopeias as an additional control mechanism for particulates and other defects in sterile injectable products. This unit level inspection is a critical control point for removal of any visually detectable and undesirable/nonconforming units to ensure overall batch quality. But there are many dosage forms that make it challenging to detect common defects such as visible intrinsic or extrinsic (foreign) particulate matter. This can be due to product formulation or container type.

These difficult-to-inspect products are not able to take full advantage of the detection and removal process (notably for particulate matter) that is provided by an effective 100% in-process inspection. Therefore, undetected visible particulates may be present in the batch. Final acceptance sampling, i.e., acceptable quality limit (AQL) inspection, may not meet pharmacopeial or regulatory agency expectations. In a worst-case scenario, particulate matter in difficult-to-inspect product goes undetected by both 100% and final AQL inspection and is then released to market. *Technical Report No. 79: Particulate Matter Control in Difficult to Inspect Parenterals* focuses on a lifecycle approach to supplemental or destructive testing methods as part of a robust difficult-to-inspect product quality process for parenterals.

Examples of difficult-to-inspect dosage forms include products such as opaque and deeply colored solutions, lyophilized cakes, powders, concentrated suspensions and emulsions. Examples of difficult-to-inspect container types include amber vials, plastic syringes, blow-fill-seal ampoules, flexible bags and specialty containers such as some cartridges and medical devices. Difficult-to-inspect products such as these require some form of supplemental analysis or destructive inspection or testing and monitoring to ensure the product meets not only the USP definition of "essentially free from visible particulates," but also the harmonized subvisible particle acceptance criteria found in the USP, Ph. Eur. and JP. To accomplish this, a lifecycle management approach that includes data from destructive inspection testing using a small sample from each batch along with a robust monitoring/trending strategy is essential in detecting, identifying and minimizing particulates.

Inspection Control and Monitoring

Control of visible defects requires inspecting each unit to remove noncompliant ones; 100% visual inspection is not the only point where product quality is assessed. A robust inspection process also includes a final check of lot quality. Here, a sample from accepted units is tested again prior to lot release. For difficult-to-inspect products, supplemental testing is also performed as required. Inspection results (defect counts or rate) are compared against historical values (reject analysis and trending) in order to ascertain that the process remains in control.

These additional functions are expected and referenced in USP <790> and <1790>. In <790>, "a complete program for the control and monitoring of particulate matter remains an essential prerequisite" when using acceptance criteria. USP <790> focuses on visible particles, but the requirements associated with particle defect control and monitoring should be extrapolated to include other defect categories/classes to ensure all aspects of the parenteral manufacturing process are evaluated for abnormal results or special cause influences—an expectation of GMP.

AQL inspection involves sampling inspected units and performing a quality control inspection to infer, at minimum, the overall batch quality in terms of critical, major and minor defect rates. Additional categories (such as particulates) may also have acceptance criteria associated with the inspection; USP <790> testing can be performed as part of this inspection. Sample size and acceptance criteria should be based on ANSI/ASQ Z1.4 (or ISO 2859-1) and AQL ranges for these categories are suggested in USP <1790>. The acceptance

number for critical defects is commonly set to zero. Alternative sampling plans with equivalent or better protection are also permitted. This AQL inspection provides continuous monitoring of the visual inspection process. Any defects found in the AQL inspection should be reviewed to determine if the visual inspection process is deficient or if the missed defects can be explained by the probabilistic nature of inspection. The detection of any critical defect is generally considered a failure with further investigation and lot remediation (i.e., reinspection) expected.

After lot quality has been evaluated, all defects found inspections should be summarized into logical groups and compared against historical results and other factors (reject analysis and trending). This provides an opportunity to determine if any batch has abnormal defect rates compared to historical batches. When batches exhibit abnormal defect rates, an investigation should determine if the normal inspection process can handle the increased defect rate(s) and if this is a special cause variation for which a CAPA should be undertaken to improve the process.

There are many considerations that must be addressed in order to have a compliant 100% visual inspection process. At the same time, an obligation exists to verify the effectiveness of that inspection, and to use the data collected to continuously improve inspection processes.

Container Closure Integrity Testing

Container closure systems should maintain the sterility and product quality of their contents throughout their shelf life. Container closure integrity testing boasts a long history, but discussion has been heightened by two developments since 2016: USP <1207.1> Package Integrity Testing in the Product Life Cycle – Test Method Selection and Validation and the EU Annex 1 draft. Both have stimulated a broad discussion on future implementation of container closure integrity testing. The short statements in Annex 1 still require some interpretation, compared to the very detailed USP recommendations, yet they may seriously impact current practice. The new requirement for routine deterministic testing of a sample from every lot of conventional containers (those not fusion-sealed) by a method other than visual inspection will require new testing or increase the number of samples for testing. Traditional tests like blue dye/microbial ingress testing typically involve tens of samples, while commonly used acceptance sampling plans typically require testing hundreds of samples, depending on the size of the batch.

Many different methods are available to perform container closure integrity testing. USP <1207> divides the methods into deterministic and probabilistic categories. Some of the most common deterministic methods used today include:

- Electrical conductivity and capacitance test/high voltage leak detection
- Spectroscopic methods/laser headspace analysis
- Vacuum decay
- Mass extraction
- Pressure decay

Register Now for PDA's 2019 Events

MARCH

18 **Pre-Filled Syringes Interest Group Meeting**
Venice, Italy | *pda.org/EU-IG-PFS19*

18-22 **2019 PDA Aseptic Processing – Option 2** ■
Week 2: April 15-19
Bethesda, MD | *pda.org/2019Aseptic2*

19-20 **2019 PDA Europe Parenteral Packaging**
Venice, Italy | *pda.org/EU/parpack2019*

21 **Container Closure Development**
Venice, Italy | *pda.org/EU/CCD2019*

21 **Packaging Science Interest Group Meeting**
Venice, Italy | *pda.org/EU-IG-PS19*

21-22 **Container Closure Integrity Testing**
Venice, Italy | *pda.org/EU/CCI2019*

21-22 **Extractables & Leachables**
Venice, Italy | *pda.org/EU/EL19-spring*

21-22 **Test Methods for Pre-filled Syringe Systems**
Venice, Italy | *pda.org/EU/TestPFS19*

25-29 **Freeze Drying in Practice**
Osterode am Harz, Germany | *pda.org/EU/FDP2019*

26-27 **Temperature Controlled Distribution**
Voorhout, The Netherlands | *pda.org/EU/TCD2019*

26-28 **Validation of Moist Heat Sterilization Processes – Option 1** ■
Bethesda, MD | *pda.org/2019MarVMH*

27-28 **Strategies for Formulations Development – How to Get the Right Data in the Right Amount at the Right Time**
Bethesda, MD | *pda.org/2019SFD*

APRIL

8-12 **QA/QC Training Course Series – Option 1**
Bethesda, MD | *pda.org/2019QAQC1*

15-17 **Fundamentals of Aseptic Processing – Missouri Valley**
Tonganoxie, KS | *pda.org/2019MissouriFundAP*

23-24 **2019 PDA Visual Inspection Forum**
Washington, DC | *pda.org/2019Visual*

25-26 **An Introduction to Visual Inspection – Option 1**
Bethesda, MD | *pda.org/2018VisualIntro*

29-2 **Fundamentals of Aseptic Processing – Option 3** ■
Bethesda, MD | *pda.org/2019AprFundAP*

MAY

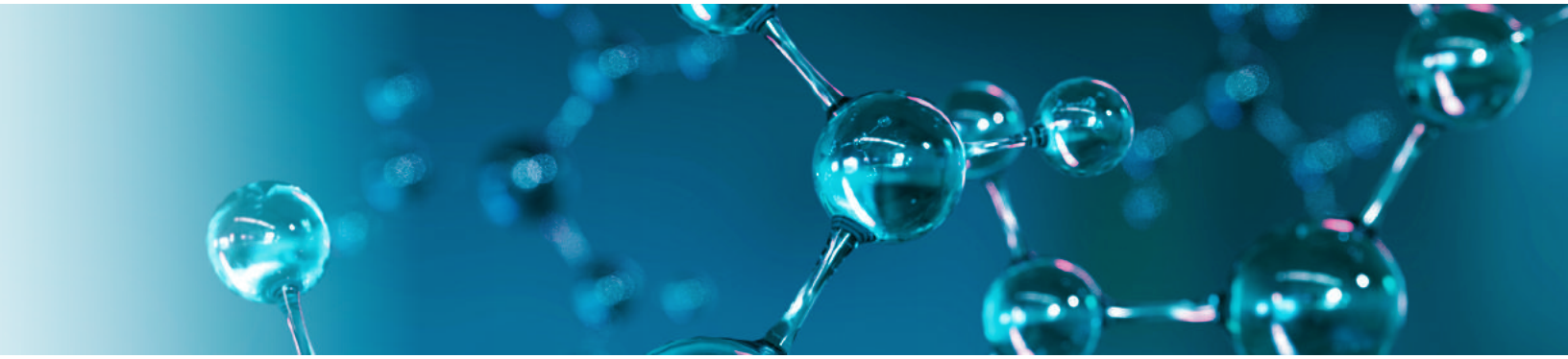
6-10 **2019 PDA Biopharmaceuticals Week**
Long Beach, CA | *pda.org/2019BiopharmWeek*

CONNECTING PEOPLE SCIENCE AND REGULATION®

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

@PDAOnline | **LinkedIn.com/company/PDA** | PDA Connect℠ **community.pda.org**

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



6-10 2019 PDA Lyophilization Training Course Series
Bethesda, MD | *pda.org/2019LyoCS*

13-17 2019 PDA Aseptic Processing – Option 3 ■
Week 2: June 10-14
Bethesda, MD | *pda.org/2019Aseptic2*

15 Understanding Pharmacopoeias
Geneva, Switzerland | *pda.org/EU/UnPharma*

16-17 2019 PDA Europe Pharmacopoeia Conference
Geneva, Switzerland | *pda.org/EU/pharma2019*

20-24 PDA Quality Risk Management Certificate Program – Option 1
Bethesda, MD | *pda.org/2019QRM1*

22-23 An Introduction to Visual Inspection: A hands-on course
Berlin, Germany | *pda.org/EU/IVI19-spring*

22-23 Mastering Automated Visual Inspection
Berlin, Germany | *pda.org/EU/AutoVI2019-spring*

22-23 Modern Polymer Pharma Packaging
Berlin, Germany | *pda.org/EU/PMP19*

22-23 Why Quality Culture? More Success by Reducing Human Errors
Berlin, Germany | *pda.org/EU/quality-culture2019*

24 Visual Inspection Interest Group Meeting
Berlin, Germany | *pda.org/EU/IGVisual2019*

29-30 Isolator Technology
Bethesda, MD | *pda.org/IsoTech1*

30-31 PDA Quality Culture Assessment Tool and Training – Option 1
Bethesda, MD | *pda.org/2019QCT1*

SPOTLIGHT ON:

2019 PDA VISUAL INSPECTION FORUM

April 23-24 2019 PDA Visual Inspection Forum
Washington, DC | *pda.org/2019Visual*

April 25-26 An Introduction to Visual Inspection
Bethesda, MD | *pda.org/2018VisualIntro*

Denotes laboratory courses taught in Europe.
■ This course is taught in PDA's U.S. Manufacturing Training Facility.

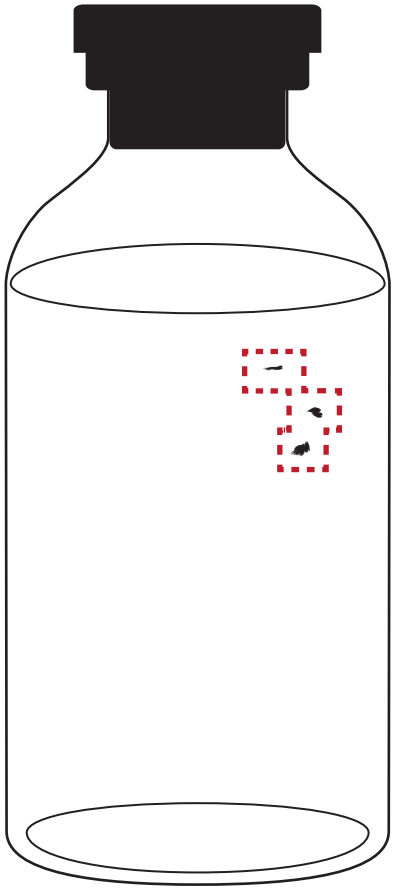
These methods are most suitable for in-line, 100% inspection, or benchtop instruments for development or testing a statistical sample from the batch.

During method development, a preliminary method is chosen and qualified. Target acceptance criteria and leak testing parameters should be established and optimized. USP <1207.1> qualification trials should be performed to demonstrate that the method can pass validation. Positive and negative controls need to be created for the test in order to be compliant with regulations. The controls should be designed in accordance with the container closure system design, materials of construction, potential package failure modes and impact to product contents on test results. Container closure integrity test methods must be validated for the specific drug-product package. The validation of the leak test method is required to demonstrate test method precision, accuracy, range, robustness and detection limit.

Conclusion

The methods used to perform visual inspection and container integrity testing continue to evolve along with ever-changing compendial and regulatory expectations. Keeping current in these developments is critical in order to implement and maintain a compliant inspection process and consistently manufacture and deliver high-quality injectable medicines.

[Editor's Note: The *PDA Letter* editors thank the planning committee behind the *2019 Visual Inspection Forum* for contributing this article**].**



pda.org/calendar

2019 PDA EUROPE

PDA Exchange Series

Meet, Exchange and Connect with Professionals from Related Fields and Expand you Knowledge!

Pharmaceutical Freeze Drying Technology

Particles in Injectables

24-25 SEPTEMBER 2019
BERLIN, GERMANY
EXHIBITION: 24-25 SEPTEMBER 2019
EDUCATION & TRAINING: 26-27 SEPTEMBER 2019

CONNECTING PEOPLE SCIENCE AND REGULATION®

REGISTER BEFORE 28 JULY AND SAVE UP TO €200!

The Challenges of Visually Inspecting IV Bags

Florian Krickl, Vitronic

Is there a common technical standard for automated visual inspection in difficult-to-inspect parenteral products? Talk with any quality manager or project engineer in the pharma manufacturing sector and they will tell you that there are a number of processes where inspection results often do not meet the expectations. As long as there is no independent standard defining the quality of automated visual inspection, however, inspection results can vary significantly case by case. This is a particular concern for IV bags.

The top two main concerns? Too high reject rates and defects not reliably detected. Case in point: Widening the tolerances of the measuring limit usually leads to a high probability of defect recognition but also results in a larger share of false rejects. On the other hand, narrowing the tolerances might result in unrecognized defects in addition to a smaller number of false rejects. Experience shows that each inspection task and process environment has its optimum setting that hits both the high value of detection probability and an acceptable reject rate.

So, what are the typical characteristics of IV bags that make it so difficult to conduct automated visual inspection?

- Flexible body: Many different influences, like shadows, light reflections and undefined air bubbles, increase the trouble distinguishing between particles/failures and acceptable influences of the packaging

Want to learn more? The author will present a poster on this topic at the *2019 PDA Visual Inspection Forum*

- Nongeometric flat shape: Dynamic spinning cannot be applied because the oval shape prevents a cyclic vortex of the fluid; hence, container inspection needs to be conducted in a static state
- Preprinted foil: Printed areas (information about ingredients and the pharmaceutical company, logos and/or variable data and codes) may disturb visual inspection; particles completely covered by print can barely be detected by automated visual inspection, and particles partly covered might be detected but are subject to misinterpretation
- Bag size: The inspection area of IV bags is usually large due to the large volume; the available resolution for the particle inspection is low compared to small inspection areas when the camera sensor is unchanged

In many filling and packaging processes, no real alternative to automated visual inspection exists. So, inspection suppliers must come up with innovative solutions for these challenges. Following are some recommendations to include in a toolkit for visual inspection of IV bags.

Start with the flexible body. Shadows, light reflections and undefined air bubbles are approached with a sound arrangement of illumination, sample positioning and appropriate background.

Many of the different failure classes (e.g., particulates, print failures, failures of the material or seam) require an individual illumination scenario (**Figure 1).** Ultimately, variations of backlight, incident light or light fed from the side is necessary to create the ideal situation for inspection with as few negative influences from the flexible body and corresponding effects as possible.

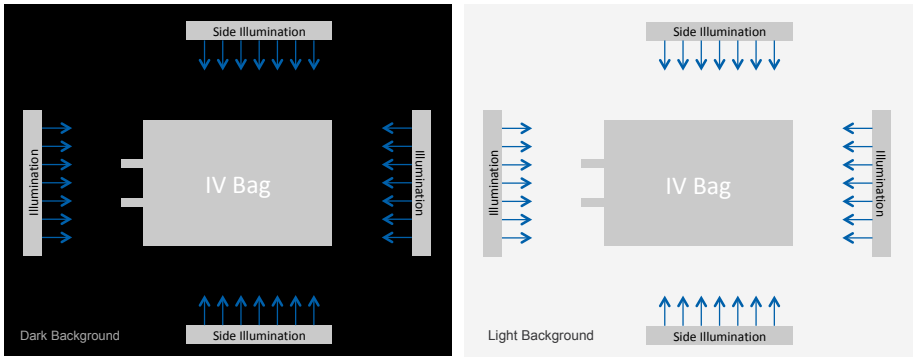


Figure 1 Different Illumination Variations

Depending on material and shape of the bag, different illuminations are combined with dark or light backgrounds; additional filters may help avoid disturbances by shadows or light inhomogeneity

Sequential acquisitions, in combination with different illumination setups, may be necessary to conduct a holistic inspection. Plus, particulates consisting of different materials and shapes may require different methods of filtering, and different background materials can be necessary for particle identification and separation. When combined appropriately, these variations can result in a complex playground of options for a quality inspection.

Static Inspection: Good or Bad?

Due to the flat shape of the bag, spinning methods cannot be applied and the inspection must be done in a static product position. But what then is necessary for inspection? Ideal illumination and positioning of the bag are, of course, essential preconditions. A stable recognition of particles and differentiation of particles from air bubbles and preprint can only be realized through sharp classification and fine-tuning in several iterations. This procedure is only mastered when the hardware and software of the inspection system are aligned with the requirements of the process environment.

There are also side benefits to static inspection, such as the need for a single picture instead of multiple pictures in dynamic inspection, which leads to reduced data volume and cycle times. Additionally, the mechanics for spinning and vibration are not required.

> **Whichever inspection solution is chosen, a number of requirements remain necessary**

Printing Can Disguise Particles

Particles completely covered by print can barely be detected with a camera perspective from top. A camera view from the side does not help much due to seams and the fluid itself.

Here, particle inspection concentrates on the gaps between the print and characters. Besides illumination and background techniques, an intelligent algorithm is needed to identify the print position on the bag as precisely as possible. By identifying the print location, the software can better distinguish between print and particle **(Figure 2).** Locating the position of individual characters is especially difficult on IV bags due to their flexibility, which means the position of the character varies with each bag. This is not only demanding for the algorithm but also for the parameter settings and the classification. Still, in ideal configurations, particles partially covered by single characters can be realistically identified.

High Resolution Cameras Can Help

The resolution of the camera depends on the required particle size or failure size to be detected. Because the inspection area of IV bags is usually large, either a combination of several camera systems or a high-resolution camera can be used. Both are available with individual advantages and at individual cost.

Whichever inspection solution is chosen, a number of requirements remain necessary. Multiple illumination and filter techniques, different background colors, sensor resolutions and refined algorithm sets can ensure good inspection results in most applications **(Table 1).**

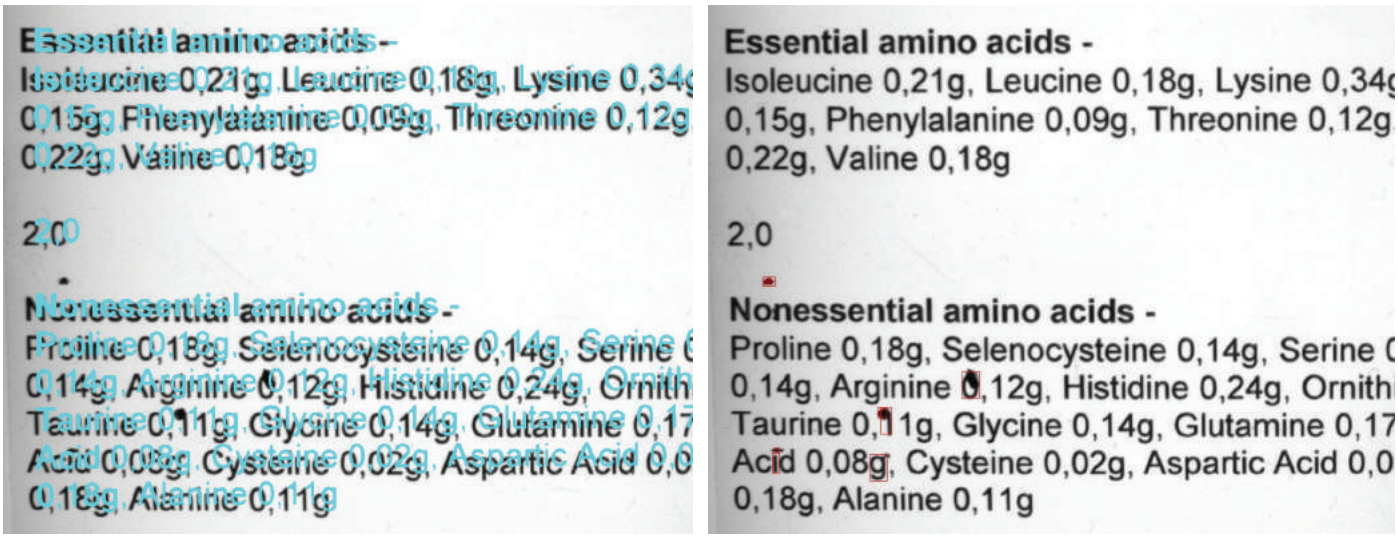


Figure 2 Before and After Analysis of Preprinted Label

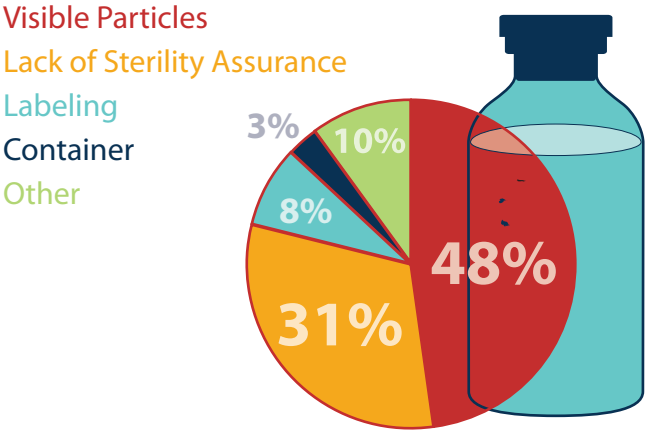
On the left, due to the flexibility and waviness of the surface of IV bags, the detected print position differs strongly from the master sample. Without intelligent processing, the print contour is not clearly defined and particles cannot be located. Now, on the right, after processing and alignment of the print with the master sample even partly covered particles can be detected.

Table 1 Overview of Challenges and Measures for Visual Inspection of IV Bags

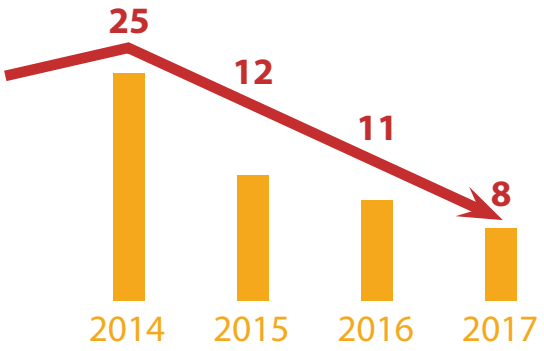
Usual Challenges of Inspection of IV bags	Some appropriate Measures and Methods
Flexible body provokes: • Undefined shadows and light reflections • Undefined air bubbles with problems to distinguish between bubble and particle	Adequate measures usually are: • Different illuminations combined with background sets • Sequential acquisitions with different illumination and filter set-ups
• Nongeometric flat shape requires automated visual inspection in static state (spinning is not applied)	• Preferably reproducible and even presentation of the product for inspection • Alignment of whole inspection set-up with the individual process requirements • Mastering and fine tuning of classification process
Printed areas disturb particle inspection: • **Particles completely covered** by print cannot be detected in static state • **Particles partly covered** by print	• Illumination and background techniques as mandatory prerequisites • Intelligent algorithm to precisely identify the position of the print, even in unreproducible flexible body • Mastering of classification and fine tuning of measuring limits
Large volume requires a large inspection area.	Adequate resolution of one/several camera(s)
Other individual challenges are: • Material inhomogeneity • Detection of particles in port areas • Detection of particles in seam areas	• Material inhomogeneity may be handled by classification and illumination/filter techniques • Particles in not visible areas of the bag may be moved to visible areas by tilting prior to inspection process

Continued at bottom of page 41

Can We Achieve "0" Defects for Visible Particles?



From 2010 to 2017, **48%** of sterile drug recalls were due to visible particles



Drug recalls due to visible particles hit a peak in 2014 and have dropped from **25** in 2014 to **8** in 2017

In 2014, USP released <790> Visible Particulates in Injections, which has helped reduce visible particulate-related recalls.

But More Can Be Done

Primary packaging components are not usually subjected to 100% inspection requirements for finished and filled product. A PDA task force is working on mitigation strategies for visible particles in primary and secondary packaging components.

Are you interested in helping? The task force continues to seek volunteers on this important initiative.

volunteer@pda.org

Source

Johns, J., et al. "Achieving 'Zero' Defects for Visible Particles in Injectables." *PDA Journal of Pharmaceutical Science and Technology* 72 (2018): 640–650.

PDA
Parenteral Drug Association

trarchive.pda.org

PDA's Technical Report Portal

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

CONNECTING PEOPLE SCIENCE AND REGULATION®

trarchive.pda.org

For licensing options contact Janny Chua at chua@pda.org

Big Data is Here to Stay

2018 PDA Manufacturing Intelligence Workshop Commands a Crowd

Aaron Goerke, PhD, F. Hoffmann-La Roche AG, and Michele D'Alessandro, Merck & Company, Inc.

Implementing big data within pharmaceutical manufacturing will require extensive collaboration. Fortunately, a 2018 PDA workshop suggests this is possible.

Last March, the *2018 PDA Manufacturing Intelligence Workshop* explored efforts to advance the use of big data in manufacturing and supply chain management. Approximately, 100 participants attended this workshop, which immediately followed the conclusion of the *2018 PDA Annual Meeting.*

The workshop provided thought-provoking keynote speakers from Amgen, Siemens, Disney and Biogen, introduced some background information on big data and reviewed the goals of PDA's big data task force. Breakout sessions focused on three areas: the Manufacturing Information Model (MIM), big data analytics for process robustness and challenges to implementing big data in a regulated industry. Each of these three sessions included group activities to help PDA's Manufacturing Intelligence Task Force develop strategies to grow big data knowledge within parenteral manufacturing.

PDA's Manufacturing Intelligence Task Force helped coordinate the *2018 PDA Manufacturing Intelligence Workshop.*

This task force falls under the PDA Manufacturing Science and Operations Program℠ (MSOP).

Manufacturing Information Model

In this track, participants acknowledged that the move to Industry 4.0 requires managing large amounts of manufacturing data, confirming the need for this body of work as a backbone of PDA's Manufacturing Intelligence Task Force.

A standard, open-source MIM will allow the industry to make manufacturing data findable, accessible, interoperable and reusable over extended periods of time and throughout the organization.

Standard open-source information models have been developed in many industries, such as the construction and process industries. In the pharma industry, the Allotrope Foundation develops data standards for scientific laboratory data.

The Manufacturing Intelligence Task Force has identified the need for an MIM for pharmaceutical manufacturers similar to other industries' information models. Such an MIM would provide a standard information architecture for manufacturing data. It would use standard terminology and be product-agnostic. An MIM enables insights to be drawn across multiple locations (internal and external suppliers) and provides faster insights from manufacturing data.

Brainstorming during the session resulted in a robust list of business use cases where an MIM would bring value. Participants agreed that increased process understanding leads to process robustness and greater yield, stability and reduction in cycle time.➤

SMA MicroParticle ICS
Non-Viable Particle Counters

THE NEXT LEVEL OF PARTICLE COUNTING

UNMATCHED ENVIRONMENTAL CONTROL

STERILE.COM

For more information, visit our website at **sterile.com/particlecounters**

vai
VELTEK ASSOCIATES, INC.

This track also highlighted the challenges of implementing an MIM that included data challenges—enabling context for historical data, ownership and governance, common data definitions and sponsorship and validation.

Potential next steps identified included communication of "data lake" best practices along with alignment on a fit-for-purpose validation approach.

Big Data and Process Robustness

In this track, 25 participants from various pharmaceutical companies, consulting firms and technology firms focused on what process data to compile, which process data can be used, and how process data should be used for monitoring and improvements. The session consisted of a case study and group exercise followed by discussion.

A case study on the evolution of a large molecule process monitoring program was presented. Merck has adopted the Pipeline Pilot software to analyze large-scale manufacturing data and report real-time process performance across its network and product portfolio.

As a group exercise, participants identified and collected the process robustness parameters from each of the unit operations within a typical biopharmaceutical drug substance and drug product manufacturing process. The group universally agreed on the need to gather and analyze all the data to improve process understanding and robustness. Yet participants expressed a concern that there remains lack of a clear understanding on how global regulatory agencies consider the use of big data for continuous improvement.

The track concluded with the consensus that industry needs to continue to gain a better understanding of the challenges of using big data to enable process robustness. All agreed that a position paper providing case studies and best practices in process robustness improvement for the industry would be a valuable document.

Big Data Meets Regulated Industry

When it comes to Industry 4.0 in a regulated environment, how should companies respond? In the third breakout session, participants reviewed the collective obstacles facing pharma in the new Industry 4.0 paradigm. These include lack of robust data governance, data lifecycle challenges and associated regulatory expectations.

> **"there is a lack of common practice when GMP and non-GMP data is mixed"**

The track then delved more deeply into Industry 4.0 concepts with a use case on applying data analytics in biomanufacturing. Key takeaways from the discussion included:

- Decision-making should be married to the data
- If the data paradigm shifts, the quality paradigm must shift as well
- Industry should look to experience from process and product monitoring to serve as examples

The track concluded with a lively debate on whether a data lake needs to be validated. Participants brought multiple views from the areas of manufacturing, business, IT and quality, such as, the data lifecycle needs to be clarified, and there is no one-size-fits-all solution when it comes to the validation approach, as it depends on use of that data. Clarity is needed on roles (balancing control and ownership in the most efficient way). And there is a lack of common practice when GMP and non-GMP data is mixed.

Following these interactive breakout sessions, the remainder of the workshop involved participants regrouping to reflect on what they learned from the earlier sessions. This led to a discussion on what additional opportunities exist in the manufacturing intelligence space that are not currently being explored by the PDA task force.

Potential use cases for the application of modern data techniques were also presented. Afterward, attendees were split into ten groups to select one of ten areas in need of deeper exploration. Recommendations were collected using online polling software. Each group spent some time identifying the risks and value propositions associated with each opportunity. At the end, each group was asked to rank the ten opportunities based on the following criteria (1= highest priority/10 = lowest priority):

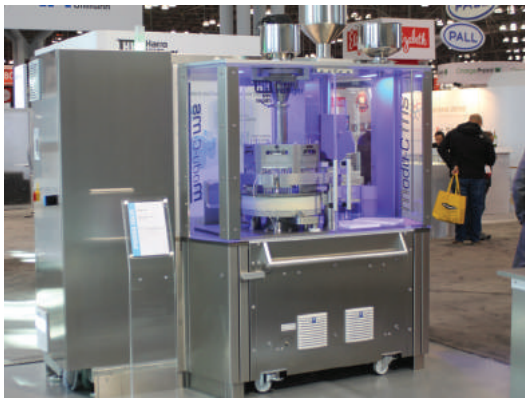
Proposed Workstream	Average Priority Rank (1-10)		
	Value Proposition	Should PDA Sponsor	I would Participate
Predictive Process Monitoring	3.56	4.20	3.53
Predictive Maintenance	**5.14**	5.44	**3.50**
Automatic Batch Release	**5.22**	5.20	3.62
Proactive Informed Decision Making	5.56	6.36	3.75
Fault Prediction	5.61	6.32	3.60
Predicting Return on Investment Failure	5.67	5.40	4.33
Visualize Data - Real Time Dashboards	5.69	5.80	**3.53**
Root Cause Investigations	5.94	6.00	3.79
Predict Quality for Real Time Release	5.94	**5.16**	4.59
Predict Impact of Raw Materials/Single-Use Systems	6.67	**5.12**	4.92

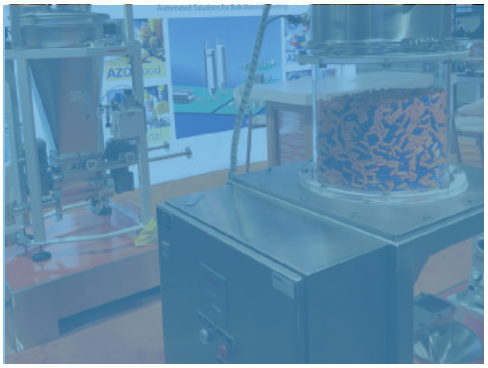
Red = 3 most favorable results in each category

Table 1 Opportunities for a Deeper Dive

experience **science** THROUGH **commercialization**

PDA Members can Register to Attend at No Cost!





PDA Parenteral Drug Association

Premier Association Sponsor

2019 APRIL 2-4

JAVITS CENTER | NYC

INTERPHEX

REGISTER FOR YOUR TECHNICAL CONFERENCE & EXHIBIT HALL PASS AT:
HTTPS://BIT.LY/2QGVZ77

1. Relative value in a cross-company workstream (value proposition)
2. Desire to have PDA sponsor a workstream in this area
3. Personal interest in participating in a cross-company workstream in that topic area

The clear preference, from the results shown in **Table 1,** was the Predictive Process Monitoring workstream. In addition to the intrinsic value of this opportunity, in post-workshop discussions, it was realized that this workstream could also take advantage of the work being done by the three existing task forces, combining their output in a way that could significantly impact the industry. Synergies with the other workshop breakouts were clear, and the task force plans to align its next steps across the workstreams as a key output.

In closing, the significant number of participants, their active interest and participation, the robust discussions and identification of specific use cases/outcomes to be further pursued all underscore the timely opportunity presented by the Manufacturing Intelligence Task Force. A roadmap will be published shortly with specific information on where additional team participation is needed most to make this a successful industry-wide collaboration.

On The Issue
letter.pda.org

Learn more about big data in an "On the Issue" video featuring Aaron Goerke

youtu.be/U-3v4lH085U

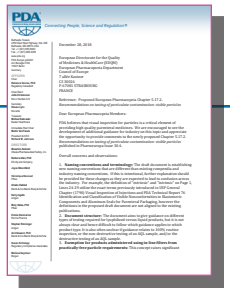
About the Authors

Aaron Goerke, PhD, has more than 14 years of industry experience in supporting bio/pharmaceutical companies in process development, manufacturing and quality systems.

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

Want to help direct the future of manufacturing? PDA's Manufacturing Intelligence Task Force seeks volunteers from other pharma companies to offer their input. If interested, email PDA's Volunteer Coordinator at volunteer@pda.org.

Eyeing Visual Inspection of Visible Particles



December 28, 2018

European Directorate for the Quality
of Medicines & HealthCare (EDQM)
European Pharmacopoeia Department
Council of Europe
7 allée Kastner
CS 30026
F-67081 STRASBOURG
FRANCE

Reference: Proposed European Pharmacopeia Chapter 5.17.2. *Recommendations on testing of particulate contamination: visible particles*

Dear European Pharmacopeia Members:

PDA believes that visual inspection for particles is a critical element of providing high quality parenteral medicines. We are encouraged to see the development of additional guidance for industry on this topic and appreciate the opportunity to provide comments to the newly proposed Chapter 5.17.2. *Recommendations on testing of particulate contamination: visible particles* published in Pharmeuropa Issue 30.4.

Overall concerns and observations:

1. **Naming conventions and terminology:** The draft document is establishing new naming conventions that are different than existing compendia and industry naming conventions. If this is intentional, further explanation should be provided for these changes as they are expected to lead to confusion across the industry. For example, the definition of "extrinsic" and "intrinsic" on Page 1, Lines 24-29 utilize the exact terms previously introduced in USP General Chapter <1790> Visual Inspection of Injections and PDA Technical Report 76 Identification and Classification of Visible Nonconformities in Elastomeric Components and Aluminum Seals for Parenteral Packaging, however the definitions in the proposed draft document are not aligned to the existing publications.

2. **Document structure:** The document aims to give guidance on different types of testing required for lyophilized versus liquid products, but it is not always clear and hence difficult to follow which guidance applies to which product type. It is also often unclear if guidance relates to 100% routine inspection, or the non-destructive testing of an AQL sample, and/or the destructive testing of an AQL sample.

3. **Exemption for products administered using in-line filters from practically-free particle requirements:** This concept raises significant concern, since it is not aligned with other current regulatory views and industry practice.

4. **Example of Quality Control confusing:** The example of Quality Control found on Page 3, Lines 16-19 is confusing as to what quantity of particle(s) may be acceptable. Reference to a Quality Risk Management (QRM) approach may make this discussion clearer.

A table with additional comments referenced to specific page and line numbers is also attached for your consideration.

Sincerely,
Richard Johnson
President and CEO, PDA
Cc: Tina Morris, Janie Miller, Ruth Miller

PDA Commenting Task Force

Andrew Walsh, CPC (co-lead)
Igor Gorsky, ValSource (co-lead)
Thomas Altmann, Ecolab
Joel Bercu, PhD, Gilead
Alfredo Canhoto, ProPharma Group
Pernille Damkjær, Novo Nordisk
David Dolan, Amgen
Andreas Flueckiger, Consultant
Jessica Graham, BMS
Ester Lovsin-Barle, Lonza
Jahanvi (Janie) Miller, PDA
Mariann Neverovitch, BMS
Mohammad Ovais, Consultant
Siegfried Schmitt, PhD, Parexel
Osamu Shirokizawa, Life Scientia

pda.org/2019Visual

2019 PDA Visual Inspection Forum

Preparing for the Future of Visual Inspection

REGISTER TODAY!

PDA® Parenteral Drug Association

Don't miss the *2019 PDA Visual Inspection Forum*, the most comprehensive exploration of the emerging trends and innovation transforming the field of visual inspection available. Insightful plenary sessions will explore:

- Advances in Automated Inspection
- Inspection Control Strategies
- Regulatory Updates
- Particle Identification, Investigations, and Supplemental Testing
- Difficult-to-Inspect Products

Plus, get your most-pressing questions answered by a panel of noted industry experts, including:

- **John D. Ayres, MD**, *Pharma Safety Solutions, LLC*
- **Roy T. Cherris**, *Bridge Associates International & InQuest Science LLC*
- **Markus Lankers, PhD**, *MIBIC GmbH & Co KG*
- **Robert J. Miller**, *Pfizer Inc.*
- **John G. Shabushnig, PhD**, *Insight Pharma Consulting, LLC*
- **Romain Veillon**, *GSK Vaccines*
- **Rick Watson**, *Merck & Co., Inc.*

EXTEND YOUR STAY! Stay after the Forum to attend the popular training course, *An Introduction to Visual Inspection*, taking place **April 25-26** at PDA's manufacturing training facility in Bethesda, MD.

Learn more and register today at pda.org/2019Visual

CONNECTING PEOPLE SCIENCE AND REGULATION®

APRIL 23-24, 2019 | WASHINGTON, DC
EXHIBITION: APRIL 23-24
AN INTRODUCTION TO VISUAL INSPECTION TRAINING COURSE: APRIL 25-26
#PDAVisual

Vaccines, Biosimilars Share Commonalities

Peter Makowenskyj, G-CON Manufacturing

On the eve of the 18th century, **Edward Jenner** inoculated the first patient in the world with a recognized vaccine. Four centuries later, at the dawn of the 21st century, legislation to allow for biosimilars was passed.

Two different specialties. Yet each face similar challenges when it comes to meeting regulatory and lifecycle requirements.

As part of its inaugural *Biopharmaceuticals Week,* PDA is bringing together industry leaders from two seemingly disparate modalities in the *2019 PDA Biosimilars and Vaccines Conference: Lifecycle Similarities and Challenges*. While biosimilars and vaccines are rarely examined under the same light, this conference will address some of the most pressing industry topics seen through similar and dissimilar lenses. The meeting will kick off with a discussion between experts from both fields about their respective approaches to product comparability and similarity. Each will talk about how their field manages product consistency throughout the product lifecycle. The conference will then break into concurrent tracks on lifecycle management and product comparability/similarity. The first day will wrap up with a second plenary session on lifecycle management in the digital era, providing a forum for discussion on the major topics of the day.

Day 2 will start off with concurrent breakfast sessions for two PDA interest groups: the Biosimilars and Vaccines Interest Groups. The Biosimilars Interest Group will review and discuss highlights of the *2018 PDA Biosimilars Workshop,* and the Vaccines Interest Group will provide an update on the group's ongoing activities around lifecycle management and vaccine specifications. The opening plenary on Day 2 harnesses the long history of vaccines combined with the quickly emerging field of biosimilars. Real-life experiences will be presented. Concurrent tracks during the day will discuss challenges, new technologies and maximizing global development, broken out by vaccines and biosimilars. The conference will conclude with a final plenary on continuous manufacturing, highlighting how this strategy is being approached through two inherently different manufacturing processes.

This conference, which concludes the *2019 PDA Biopharmaceuticals Week,* is an excellent opportunity to catch up on the latest trends and to network with like-minded colleagues.

2019 PDA Biosimilars and Vaccines Conference

Long Beach, Calif.
May 9–10
www.pda.org/2019biopharmweek

The Challenges of Visually Inspecting IV Bags continued from page 31

In some aspects, there are similarities between visual inspection for IV bags and other filling processes. Many inspection solutions can generate acceptable results, yet each process has its own particularities. Achieving good results requires pairing practical experience with innovation. Then, available methods can be adapted to present conditions and improved for the specific process environment.

About the Author

Florian Krickl has more than 20 years of experience in various functions in medical, environmental technologies and electronics industries. He is currently Product Manager for Industrial Automation at Vitronic.

Implementation Proves Parametric Release Possible

Increased Process Understanding Drives FDA Approval of Parametric Release

James Assini, Sanofi

For terminally sterilized product, parametric release can be granted by regulators when firms have demonstrated thorough control of their sterilization processes using defined critical process controls. This enables the release of product for commercial sale without performing sterility testing on each product lot.

Not having to perform sterility testing on each lot saves 14 days of incubation time along with testing materials and the need for QC analysts to inoculate the samples into media and perform readings. The product lot can be released with a successfully executed batch record and documentation of acceptable sterilization cycles. In addition, product previously used for testing is made available for use by the patient.

Sanofi's Ridgefield, N.J. facility was the site of a parametric release implementation

The Current Regulatory State

Both U.S. and EU regulators have aligned on parametric release. Annex 17 of the EU GMP guidelines describes parametric release as "release of a batch of terminally sterilised product based on a review of critical process control parameters rather than requiring an end-product testing for sterility" ***(1).*** Furthermore, Annex 17 recognizes that a comprehensive set of in-process tests and controls may provide greater assurance of the finished product meeting specification than finished product testing alone ***(1).***

The parametric release process also meets requirements in 21 CFR 211.165(a) and 211.167(a) in the United States. The U.S. FDA published a more recent guidance on parametric release to help support industry in 2010. *Submission of Documentation of Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes* describes the submission requirements for parametric release. In 2012, FDA published a revision to its Compliance Policy Guide Sec. 490.200 *Parametric Release-Parenteral Drug Products Terminally Sterilized by Moist Heat* that describes the critical aspects of a parametric release program.

A parametric release program must demonstrate the following: thorough process understanding, process control and documentation. Process understanding is information collected from a scientifically developed terminal sterilization cycle. Process control is proven through monitoring and controlling microbial contamination at relevant points during the manufacturing process. For a terminally sterilized product, monitoring bulk drug product and components is critical because microbial contamination introduced by raw materials or components during the manufacturing process can multiply and damage the product or create endotoxins. Specific parametric release documentation includes the microbial control strategy, risk assessments, batch records and segregation procedures.

Parametric Release in Action

At Sanofi, the three-year journey to approval of parametric release for a drug product at our Ridgefield, N.J. facility resulted in increased process understanding. An external consultant, including a microbiologist who previously worked for FDA, provided fresh eyes on our processes. We chose not to rely on the classical risk assessment approach using risk ranking as is typically done in a conference room. Instead, we performed walkthroughs on the shop floor to assess our processes in use, identifying risks and areas in need of improvement. This deeper level of knowledge led us to make small improvements that resulted in large gains. Operator input also offered opportunities to simplify processes.

We did not request an FDA Type C meeting to discuss our project but did use approaches outlined in existing EU and U.S. regulatory guidances and PDA technical reports on the topic. We made the following technical changes to support parametric release:

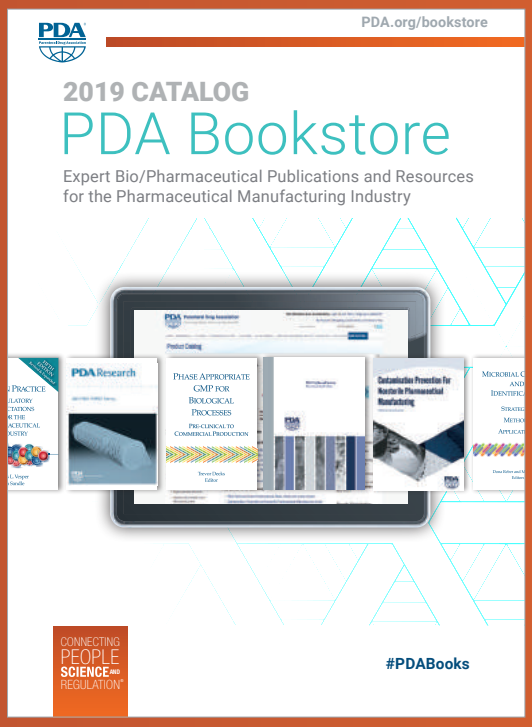
- Installed dual-temperature probes in the autoclave
- Used Class 4 chemical indicators in each autoclave load
- Enhanced physical segregation of sterilized versus nonsterilized materials
- Modified documents to incorporate the new process

We began implementation in June 2014 and submitted the Prior Approval Supplement to FDA in January 2017. Five months later, we received approval.

PDA
Parenteral Drug Association

pda.org/bookstore

The 2019 PDA Publications Catalog is Now Available



Explore the 2019 PDA Publications Catalog to see all the publications and resources PDA offers to help you stay up to date with advancements in the bio/pharmaceutical industry. PDA's offerings include a library of more than 80 peer-reviewed technical reports, a large selection of technical books and booklets, and a collection of surveys.

Edited and/or authored by industry and regulatory experts and thought leaders, these technical publications serve as practical guides and references for many topics in the industry, including:

- Aseptic Processing
- Quality and Regulatory Compliance
- Supply Chain
- Biotechnology
- Manufacturing Science
- and more!

CONNECTING PEOPLE SCIENCE AND REGULATION®

Expand your library and increase your knowledge of important industry topics!

we understand our process, equipment, and capabilities much better

In order to determine if parametric release could be appropriate, the product should not have a history of sterility failures. Fortunately, we had an existing drug product that had not experienced any sterility failures. Consistent bioburden control of the upstream process is also required, along with dependability of manufacturing equipment and autoclaves. We carefully reviewed the preventive maintenance history of our autoclaves during this process, confirming that the equipment was well maintained and performed consistently.

After completing these assessments, we understand our process, equipment and capabilities much better. We reevaluated all the microbial controls in our process, including upstream process controls. We also revisited our sterilization cycle development. These reevaluations resulted in our team gaining an increased awareness and understanding of the process.

Overall, implementation of parametric release has allowed us to get product to market faster. Before parametric release, we conducted sterility testing samples from each autoclave sterilization load with a 14-day incubation period, followed by sample reading and completion of documentation with 40 samples tested per autoclave sterilization load. After parametric release, we used the data obtained to add redundant temperature probes at the worst-case location (i.e., the drain), add chemical indicators to loads, implement additional review steps in the batch record, cease further sterility testing except for stability testing, use the same autoclave cycle, require fewer sampling interventions and reduce the number of required sampling interventions. The end result? More product was available much sooner to the patient.

Reference

1. EudraLex, Vol. 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 17, 2018 tinyurl.com/y6nfozay

About the Author

James Assini is Associate Director of Quality Assurance at Sanofi's site in Ridgefield, N.J. His expertise is in microbiological QC testing and sterility assurance/contamination control.

On the Issue Videos by the *PDA Letter*

Interviews with leading industry experts on the issues important to you

Watch the following experts:

- Roche's Aaron Goerke — Big Data
- Novartis' Christian Scheidl — Data Integrity
- U.S. FDA's Francis Godwin — Supply Chain
- U.S. FDA's Dan Mellon — Extractables and Leachables

For more information on all PDA videos, podcasts and other interviews, please visit us at www.pda.org/pdaletter

CONNECTING PEOPLE SCIENCE AND REGULATION®

Another Year of Reg Collaboration

Emma Ramnarine, Roche/Genentech

PDA has started off the first quarter of 2019 with a plethora of regulatory activities. As a member of the Regulatory and Quality Advisory Board (RAQAB), I am proud to continue PDA's leadership in collaborating with global regulators and pharmacopeias.

But first, I want to welcome PDA's new Director of Regulatory Affairs, **Ruth Miller**. I, along with the rest of RAQAB, am excited she is bringing her broad experience base to PDA and look forward to working with her as we move forward with PDA's regulatory agenda in 2019.

First, PDA collected comments through Feb. 28 for the PIC/S revised draft guidance, *Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments.* PDA happily assisted with consulting with stakeholders on specific questions relating to the proportionality, clarity and implementation of the guidance's requirements. And speaking of data integrity, do not forget to register for the *2019 PDA Data Integrity Workshop* following the *2019 PDA/FDA Joint Regulatory Conference* in September.

PDA has also been collecting data from a survey on technology transfer practices. These results will be summarized in the Technology Transfer Interest Group session at the *2019 PDA Annual Meeting.* The editors of the *PDA Letter* also plan to publish these results in a future *PDA Letter* InfoGraphic.

As far as technical reports, PDA plans to remain prolific in this space. One of the technical reports to be published this year touches on a hot topic for both industry and regulators: product lifecycle and post-approval change management. It will supplement ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management,* and the latest global thinking and concepts on post-approval change management by providing practical application solutions and examples. It has been a unique challenge for the technical report team to author a report for such a dynamic and constantly evolving topic—it has surely tested their ability to adapt!

Another eagerly anticipated technical report covers regulatory requirements for excipients. In 2011, the EU Falsified Medicines Directive required manufacturers to use formalized risk assessments to ensure excipients are suitable for use in products. We expect this technical report to clarify this area. I can tell you that the technical report team has been hard at work with teleconferences even going into the evenings for our U.S. colleagues!

Of course, PDA does not plan to rest on its laurels when it comes to working with regulators. You can expect to see continued engagement, commenting, new task forces and other global regulatory activities as we continue into 2019.

PDA
Parenteral Drug Association

pda.org/EU/UPS2019

2019 PDA EUROPE

The Universe of Pre-filled Syringes and Injection Devices

Advancing Drug Delivery Systems to Improve Patients' Lives

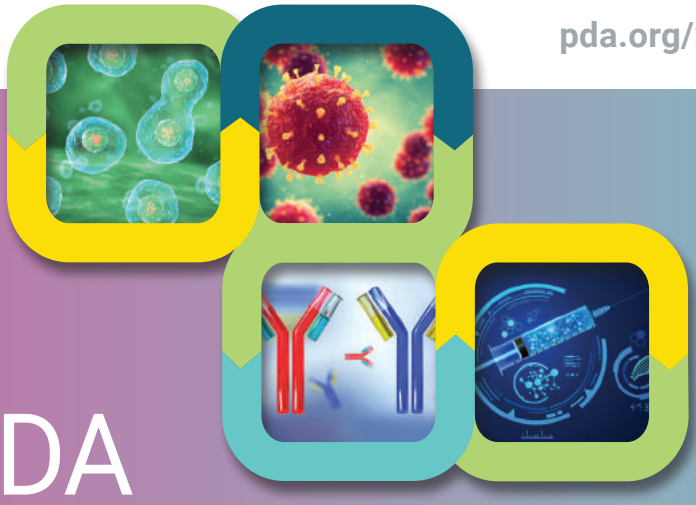
CALL FOR ABSTRACTS

22-23 OCTOBER 2019
GOTHENBURG, SWEDEN
PRE-CONFERENCE WORKSHOPS: 21 OCTOBER
CONFERENCE & EXHIBITION: 22-23 OCTOBER
EDUCATION & TRAINING: 24-25 OCTOBER

ABSTRACT SUBMISSION DEADLINE 29 MARCH 2019

CONNECTING PEOPLE SCIENCE AND REGULATION®

pda.org/2019BiopharmWeek



Register by March 22 and save!

2019 PDA Biopharmaceuticals Week

PDA® Parenteral Drug Association

Make plans to attend one, two, or all three of the events taking place during the inaugural *PDA Biopharmaceuticals Week*!

This unique week of events highlights advances, best practices, and challenges in important areas of biopharmaceutical manufacturing.

2019 PDA Cell and Gene Therapy Conference | **May 6-7** | *pda.org/2019CGT*
Through comprehensive plenary sessions and an informative breakfast session, explore the hottest topics driving the industry, including facility design, tech transfer and comparability, product characterization, the application of quality risk management principals, and much more!

2019 PDA Virus Safety Forum | **May 8** | *pda.org/2019Virus*
This one-day forum opens with a breakfast session with the Advanced Virus Detection Interest Group. Following the Breakfast Session, participate in engaging sessions on virus testing and detection, viral mitigation, virus clearance, and practical considerations and applications for viral safety challenges.

2019 PDA Biosimilars and Vaccines Conference: Lifecycle Similarities and Challenges | **May 9-10** | *pda.org/2019BVConf*
End the week with two full days of plenary sessions and concurrent tracks covering both biosimilars and vaccines. Gain insight into the parallels between the manufacture, supply, and quality of biosimilars and vaccines.

Take advantage of special multi-event registration discounts! Save 10% when you register for two events and save 15% when you register for all three events.

Learn more and register at pda.org/2019BiopharmWeek

CONNECTING PEOPLE SCIENCE AND REGULATION®

MAY 6-10, 2019 | LONG BEACH, CA
EXHIBITION: MAY 7-9
TRAINING COURSE: MAY 8
#PDABiopharmWeek