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PDA Letter

Volume LVI • Issue 3 www.pda.org/pdaletter May/June 2020

Visual Inspection Practices of Cleaned Equipment 20

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May/June 2020 PDA Letter

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Visual Inspection Practices of Cleaned Equipment: Part I

Walid El Azab, STERIS, and Stephane Cousin, GSK Vaccines

Regulatory and compendial guidelines require that manufacturers confirm process equipment is visually clean following a cleaning operation. Recently, an industry survey showed that visual inspection practices for cleaned equipment differ among manufacturers. At the same time, the survey indicated that while practices and even terminology may differ, this can be accepted by regulators provided processes are well documented.

Cover Photo courtesy of Steris

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CMO Works Around the Clock to Produce COVID-19 Meds

Rebecca Stauffer, PDA

Recently, three clients of contract manufacturer Berkshire Sterile Manufacturing (BSM) had a special request for the CMO. Could BSM manufacture three sterile drugs that would serve as treatments for COVID-19? And, instead of the normal three- to six-month turnaround time, could they do it in four weeks?

The PQL Team Part III: Staying Ahead

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

The PQL role is established, a team of PQLs built, and a capability/skills matrix developed to help the PQLs succeed and grow. The next step involves expanding their skillsets by applying additional lean concepts that will move PQLs toward continuous improvement and "staying ahead."

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New Vial Tech Shows Promise for Pharma Productivity

Dawn Watson and Jeff Cremi, Merck & Co., Inc.

Advances in pharmaceutical glass packaging offer advantages for both patients and manufacturers, but the potential of new innovations will not be reached without rigorous testing and line trials to confirm their benefits.

PDA Letter

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The PDA Letter is published 6 times per year in print, 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 | Sterility Test Failure Investigations**
Dennis Guilfoyle, PhD, discusses sterility test failure investigations at the 14th Annual PDA Global Conference on Pharmaceutical Microbiology.

pda.org/letter

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2020 PDA Advanced Therapy Medicinal Products Month

WEBINAR SERIES

Throughout the month of June, PDA will be bringing you convenient, information-dense webinars focused on breakthrough therapies, novel technologies, and the practical challenges of global regulatory strategies in this rapidly changing field.

WHEN: 11:00 a.m. ET every Tuesday and Thursday in June

WHERE: From the convenience of your own computer or mobile device.

WHAT: A series of **nine webinars** featuring industry and regulatory experts. They will be discussing the current state of the science and exploring the real-world challenges companies are facing and solutions that are being implemented. Each webinar includes ample opportunity for a live Q&A with the presenters through the easy-to-use chat function.

COST: $200 for each individual webinar.

As part of PDA's ongoing commitment to the future of the pharmaceutical industry, we are ensuring that our high-quality programming is delivered in a format that is accessible, convenient, and cost-effective for you and your companies.

Be sure to take part in this unique and informative month-long event!

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

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PDA
Parenteral Drug Association

go.pda.org/Standard001

PDA Releases first ANSI/PDA Standard

PDA, who is accredited by the American National Standards Institute (ANSI) as a Standards Developing Organization, is pleased to announce the release of its first Standard, **ANSI/PDA Standard 001-2020 Enhanced Purchasing Controls to Support the Bio-Pharmaceutical, Pharmaceutical, Medical Devices and Combination Products Industries**, which is now available for purchase in the PDA Bookstore.

This new consensus standard promotes awareness of purchasing control requirements for specific material, components, product, or services throughout a product lifecycle. It also highlights the responsibilities for compliance at all stages, and how these duties are shared throughout the entire organization, with final responsibility falling to the management of the company.

The need for risk-based processes and having an independent Quality Unit are also discussed in this standard. Recommendations for specific procedures are outlined

This Standard is intended to expand on the requirements already defined under FDA regulations and should be viewed only as recommendations.

Digital Item No. 60000 | **PRICE Member: $180 | Non-Member: $325**

For more information or to purchase, visit go.pda.org/Standard001

ANSI

As an ANSI accredited Standards Developer, PDA has met the guidelines set forth in the ANSI Essential Requirements: Due process requirements for American National Standards that include openness, consensus vote, due process, lack of dominance, balance, public review/consideration of view and objections, an appeals process, and compliance with the ANSI policies and administrative procedures.

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Visit *pda.org/bookstore* to see all of the technical books and resources PDA has to offer.

PDA and *PDA Letter* Plow Ahead

Rebecca Stauffer

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It is the start of summer and many of us remain at home to work. Those who are reporting to their offices or facilities are following strict social distancing and preventative measures.

The *PDA Letter* recognizes that many readers continue to work hard at ensuring there is a stable supply of sterile drugs and supporting efforts to develop new vaccines and treatments for COVID-19. While this pandemic is affecting our community, new Letter content will be open access to both members and nonmembers. We continue to publish articles of interest to the industry weekly on a variety of topics, from environmental monitoring to new production technologies to risk management strategies and more.

The second episode of *GMP Tales,* the *PDA Letter* podcast will also be released shortly.

I also encourage readers to review the slate of upcoming virtual offerings from PDA. Both the U.S. and European *Advanced Therapy Medicinal Products* conferences are now online. The U.S. meeting is now a series of virtual webinars throughout the month. PDA Europe's *Quality and Regulations* conference, originally planned for Dublin, and the 2020 *PDA Annual Meeting* are both online-only, as well.

PDA Education now offers a number of online courses, both on demand and live, many of them based off our technical reports. Speaking of which, PDA continues to publish technical reports, surveys, and other publications thanks to our dedicated staff and volunteers who are not slowing down even in the midst of this pandemic.

In April, PDA launched its first ANSI standard, *PDA Standard 001-2020: Enhanced Purchasing Controls to Support the Bio-Pharmaceutical, Pharmaceutical, Medical Devices and Combination Products Industries.* More standards are in the pipeline as well.

Even though I am not able to see my readers in person, I want to extend a virtual thanks and urge readers to continue checking out the *PDA Letter* website and the main PDA site for the latest resources to help the industry as it moves ahead.

New Website for PDA Foundation Launched

On June 1, PDA launched a new website for the PDA Foundation, a 501(c)(3) nonprofit founded in 1997 to help support PDA and other industry activities. This new website makes it easier for industry stakeholders to donate money for various activities, as it includes an online processing system.

The PDA Foundation seeks donations to support PDA's education and research activities in the advancement of pharmaceutical science. Previous significant donations included new equipment used for PDA Education courses at the PDA Training and Research Institute in Bethesda, Md. and support for research into particle loading on elastomeric closures.

The PDA Foundation's website can be found here: https://www.pda.org/about-pda/foundation.

PDA Publishes First ANSI Standard

PDA published its first standard, ANSI/PDA Standard 001-2020, Enhanced Purchasing Controls to Support the Bio-Pharmaceutical, Pharmaceutical, Medical Devices, and Combination Products Industries, in April.

ANSI/PDA Standard 001-2020 is aimed at all personnel involved in the procurement, purchasing, or sourcing decisions within health care product manufacturing organizations. It makes clear that those who make the final decisions are responsible for the quality of the product, not just those in the manufacturing and quality units.

PDA is currently working on advancing five other standards.

ANSI/PDA Standard 001-2020 is available at the PDA Bookstore and costs $325.00 ($180.00 for PDA members and government employees).

PDA Board of Directors Changes

In light of the appointment of **Glenn E. Wright** as Vice President of Scientific and Regulatory Affairs, he has vacated his position as treasurer on the PDA Board of Directors.

Melissa Seymour, Biogen, Inc., will step in as treasurer while Director **Emma Ramnarine,** Genentech/Roche will fill Seymour's term as secretary.

Stephan Rönninger, PhD, Amgen, will complete Ramnarine's term as Director.

Glenn Wright

New Advisory Board Formed

Recognizing the growing importance and impact of cell and gene therapy products, PDA recently launched the Advanced Therapy Medicinal Products Advisory Board.

This new advisory board will oversee PDA projects and interest groups involved with cell/gene/tissue-engineered therapies, i.e., advanced therapy medicinal products. The advisory board will also provide guidance to PDA in the development of events, education courses and technical publications to assist companies developing these innovative products.

Michael Blackton, Vice President Global Quality, Adaptimmune, LLC, and **Stephan Krause,** PhD, Head of Product Quality, AstraZeneca Biologics, have been appointed to form and lead the new advisory board.

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Guest Editorial: Expect Drug Shortages to Get Worse

Martin VanTrieste, President & CEO, Civica Rx

As the current events surrounding coronavirus continue to unfold, we should expect drug shortages to get worse. It is too late to prevent drug shortages during an ongoing pandemic, and we are reaping what we have sown. By allowing essential generic medicines to become commodities and the pharmaceutical supply chain to globalize, in large part leaving the United States, we have created the perfect environment for drug shortages to develop.

Most of the essential medications related to a coronavirus infection needed to treat the very ill are the old standbys, such as antibiotics, diuretics, pressor medications, medications to treat heart failure, etc. As a society, we encouraged the price to be driven down to unsustainable levels ("The Race to the Bottom"). For example, some sterile injectables are selling for U.S. $0.39 a vial, and most of these essential medicines cost less than U.S. $2.00 per container. During many public appearances, **Janet Woodcock,** MD, Director, CDER, U.S. FDA, has questioned why it is acceptable for us to expect essential sterile injectable medicines to cost less than a Starbucks coffee. Drug shortages are not limited to the U.S., though. All countries that have driven down the price of sterile injectable products to unsustainable levels experience drug shortages.

These extremely low prices have turned essential medicines into commodities, like oil. When the price of oil falls too low, oil exploration and pumping oil out of the ground halts, resulting in shortages and rapid price increases. Why should we expect anything different for essential medications from the broken economic model that we have created? This broken model creates problems beyond the ability of most units within a company to fix, including Quality, R&D, Engineering and Manufacturing. These units cannot fix the shortage problem because they cannot address the true root cause. These conclusions have also been validated in the most recent FDA drug shortage report, *Drug Shortages: Root Causes and Potential Solutions.*

This broken economic model has forced pharmaceutical supply chains to become long, complex, and fragile in order to reduce costs, creating a dependency on foreign countries for our pharmaceuticals, especially China. It has been reported widely that 80% of pharmaceuticals are dependent on raw materials, API precursors, APIs, and even drug products from China.

In addition, at unsustainable prices, there is little appetite for investment in sterile filling capacity, upgrading existing facilities, or making process improvements; instead, the available capacity is used for the most profitable products, such as branded pharmaceuticals or biotech medicines. And investments in facility maintenance, supplier development and product quality have also been reduced. The result is a complex pharmaceutical supply chain that is long and fragile, depending heavily on India and China.

I recommend two excellent books for all pharmaceutical professionals: *Bottles of Lies: The Inside Story of the Generic Boom,* by **Kathrine Eban**, and *China Rx: Exposing the Risks of America's Dependence on China for Medicine,* by **Rosemary Gibson**. Both books clearly describe the risk and results of globalization on the pharmaceutical supply chain. They are excellent reads for anyone in the pharmaceutical and healthcare industries. *Bottle of Lies* focuses on the poor quality and data integrity issues at certain Indian manufacturers and *China Rx* focuses on national security issues related to allowing China to become the world's pharmacy.

I also recommend watching a ZEMBLA documentary at https://youtu.be/z6M-tJSo_CAY.

Based on the short-term success that the generic drug industry had with globalizing its supply chains, many branded pharmaceutical companies have followed suit. Even if the API is produced in the U.S. or Europe, one must ask: where are

the chemical precursors needed to make API's sourced from?

Recently, India prohibited the exportation of 26 APIs and medications. Other countries will likely follow suit in order to protect their own citizens if coronavirus events escalate out of control. A recent STAT News article says that the test used to detect a coronavirus infection depends on a raw material from China, which is now in short supply ***(1)***.

I have the honor to lead a company called Civica Rx that was created by leading U.S. health systems and philanthropies to address drug shortages. Civica's unique business model is nothing proprietary or earth shattering but it does cost money and take resources to launch and achieve fast success. Here are the key initiatives introduced by Civica to prevent drug shortages of essential generic medications for our more than 1200 hospital members:

1. Create long-term, guaranteed contracts between health systems, Civica and our suppliers.
2. Don't buy API from China or India, when possible, and invest in shortening the complex, long and fragile supply chain.
3. Develop redundant manufacturing.
4. Create strategic stockpiles (safety stock) of medications and raw materials.

Continued at bottom of page 14

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2020 PDA Combination Products Workshop

Improve the success of your product and company with the latest advances in combination products!

Join the *2020 PDA Combination Products Workshop* to hear firsthand how dramatic growth and evolution is impacting the industry.

Take home practical guidance based on the real-life experiences of pharmaceutical and medical device professionals who are facing or have faced the same challenges as you are. Benefit from what they have learned and the solutions they have implemented during the development, approval, and lifecycle management of their drug deliver combination products.

Dive into these hot topics:

Bridging/Leveraging Existing Information	**Digital Health**	**Globalization of Combination Products**	**Generics**
Human Factors	**Reliability**	**Cross-Labeling/ Combined Use**	**Safety Reporting**

Don't miss this opportunity to interact with expert speakers and other attendees to get the important information you need to improve the success of your product and your company!

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OCTOBER 7-8

TRAINING COURSES: OCT. 7

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PDA is committed to maintaining opportunities for volunteers and individuals from the pharmaceutical industry to meet, wherever we can do so. PDA considers safety and health of event attendees as a subject of utmost importance. PDA has implemented a set of measures to protect participants and staff from potential risks related to COVID-19 as best as possible. This includes a close and regular monitoring of the situation, adherence to recommendations of health authorities and official travel warnings, precautions being implemented at our venues, and the possibility of remote presentations or virtual events.

Singapore Chapter Elects New Board via Electronic Voting

The PDA Singapore Chapter recently announced the results of the election for the chapter board.

Singapore Chapter Board 2020–2022
President: Bruce Loxley, GSK
President-Elect: Emily Cheah, Charles River Laboratories
Secretary: Andyanto Sutandar, HGP Asia/NNIT Singapore
Treasurer: Christina Chen, CAI

Members-at-Large:
Richard Chai, STERIS Corporation
Li Wei Chan, GSK
Shi Ming Chau, Johnson & Johnson
Katie Parks, Amgen
Priyabrata Pattnaik, Merck
Rama Tummala, GSK

Due to the COVID-19 situation, the election was carried out by electronic voting, the first for the chapter. The Annual General Meeting, where the outgoing board shared the previous year's events and financials along with the election results, was done by Skype—another first for the Chapter.

The 2020–2022 board brings a wealth and breadth of experience. Half of the Board Members were active Board Members and volunteers in 2018–2020 term. Chapter President Loxley is responsible for audit risk assessment preparation, audit planning and execution and reporting at GSK. President-Elect Cheah is currently the Managing Director of Charles River Laboratories Singapore (Microbial Solutions). Secretary Sutandar is a manager in the NNIT Group Life Sciences Divisions of HGP Asia Pte Ltd, Singapore, and leads HGP's Manufacturing Science and Technology service unit. Secretary Chen is Director of Operations at CAI (Southeast Asia). She has 18 years of commissioning and qualification and cGMP experience in the operation and validation of various types of equipment, manufacturing facilities, cleaning processes and process validation with various clients across Asia.

Please note that, at this time, chapter events originally planned for May will likely continue as virtual events. Where possible, the chapter is seeking an opportunity to collaborate with other chapters in the region for their coming virtual events. Check the chapter website https://www.pda.org/chapters/asia-pacific/singapore for the status of other upcoming events.

Chapter Covers New Developments in Visual Inspection

Aidan Harrington, DPS Global, and President-Elect, PDA Ireland Chapte

Visual inspection is a major topic of interest to PDA members around the world. On Nov. 22, the PDA Ireland Chapter held a meeting in Kildare focused on "Visual Inspection — Requirements, Practical Implementation and Future Technologies."

The major critical takeaways from the event cover manual inspections, automated inspections, regulatory developments, achieving zero defects for visible particles, new technologies and difficult-to-inspect products.

Manual Inspection

To meet the requirements for inspector training and qualification, separate defect sets for training, size sensitivity and qualification need to be created. The manual baseline should consider inspection conditions (e.g., station, lighting), inspector technique (e.g., pacing), individual inspector variability and person-to-person variability. When multiple container types, sizes and fill levels are used in a manufacturing facility, it may be possible to develop a bracketing approach to operational challenge sets. Acceptance criteria for manual inspection qualification criteria is strongly influenced by qualification set design.

The first step in developing a validation challenge set is to complete a risk assessment for the entire process, including component manufacturing—container, stoppers, product formulation, container filling and container handling, for example. A well-designed challenge set will ensure that automated processes are robust, and that defect detection is reliable. Including hard-to-detect defects in sets results in lower acceptance criteria.

Lower acceptance criteria should not be confused with lower process capability, however. Clear and detailed descriptions of created defects need to be included in procedures to ensure consistency over time and the ability to replace defects (e.g., written descriptions, pictures). If the created defect is not a direct copy of the natural defect, performing studies that demonstrate comparable performance for visual inspection should be considered. Having a specialized group or specially trained individuals devise sets would produce clear benefits.

Automated Inspection

With the advances in technology, many companies are exploring automated inspection. To implement an automated system, though, first requires developing a high level of competence with manual inspection. Having a thorough understanding of the product and its inherent variability is required before it can be migrated from manual to automated visual inspection. For example, a company would need to develop in-house expertise in machine vision, or it would have to rely on vender support and availability.

Should it come to selecting a vendor, having a formal process in place for commercial bid analysis allows for visual and transparent decision-making. It would also align with the desired values and culture of lean, enabling teams to emphasize a project's value to its stakeholders. One speaker relayed how one company took to the road, delivering samples door-to-door to mitigate the impact of shipment in defect samples. To limit potential false rejects due to container variability, Schott created vials with dimensions at limit of specifications (maximum, minimum and nominal) for heel radius, shoulder, push-up and bottom thickness.

Qualification maintenance was also discussed as an alternative to requalification with defect panels in an annual review process. This would only be valid if a robust inspection lifecycle process, per *USP <1790> Visual Inspection of Injections,* was followed ***(1).*** Trending of rejects over time is key: If an automated inspection method is shown to be better than the manual method, does this call into question the use of the manual method for reinspection?

Also having the capability to conduct offline investigations, that is, a mirror copy of a vision system on an offline laptop, was highly recommended.

Regulatory Developments

Defects remain one of the Top 10 reasons for drug product recalls, with more than 200 incidents since 2008. From the regulators' perspective, if you can see it, you should control it!

The quality risk management (QRM)/lifecycle approach is the key to particulate matter control—what presents a risk to patients?

Not only equipment and processes, but the human factor should be considered. Limitations and stressors should be addressed as part of the operator qualification program, which should also include fatigue studies. And QRM processes should be integrated as part of operator training.

Achieving Zero Defects for Visible Particles in Parenterals

When it comes to the topic of achieving zero defects for visible particles, PDA is involved in numerous activities. One study, initiated in 2017 by an industry cross-functional group (co-sponsored by PDA and the Pharmaceutical Manufacturing Forum), that addresses particle sources in pharmaceutical products is ongoing. Another task force is focusing on visible particles in ready-to-fill, use-and-sterilize components, glass and elastomer components and secondary packaging associated with packaging components. Outcomes from some of the studies to date have been published in the *PDA JPST* and publication of future results is anticipated.

New Technologies

The industry is rapidly evolving with respect to its manufacturing processes and advanced therapies. Inspection technologies need to evolve in parallel.

Interest in applying deep learning and artificial intelligence (AI) technologies to visual inspection is growing. Factories of the future will likely feature a vision robot unit that incorporates deep learning and AI and is integrated with factory systems. Deep learning technology will be reactive, that is, the inspection reacts to product characteristics during one batch and adapts. Continuous learning ensues from production and from operators' retraining of new defects and false rejects reduced by retraining false positives.

Difficult-to-Inspect Products

Many of those attending this meeting work primarily with lyophilized products. For these products, particles are revealed only at the surface. Organizations have developed a consistent approach with respect to destructive testing methodology (*USP <788> Particulate Matter in Injections*) and sample sizes used for lyophilized products ***(2).*** Reconstitution is typically performed in a controlled environment using a terminally filtered diluent and mixed to obtain a clear solution. While discussed, the filtration method is not used by participants; instead, the reconstituted and filtered product is examined by microscope.

While workshop participants did not have experience with other difficult-to-inspect products, **John Shabushnig** highlighted *PDA Technical Report No. 79: Particulate Matter Control in Difficult-to-Inspect Parenterals* ***(3).*** This technical report describes best practices for difficult-to-inspect parenteral product lifecycle management, destructive testing, and trending to supplement portions of the guidance given in USP <1790>.

During the Q&A portions of the meeting, participants shared their experiences with foreign regulators' expectations of visual inspection. Two participants reported that Russian inspectors had expressed a requirement for a Grade D background for inspections. Chinese inspectors envisage inspection taking place in a quiet, dark room with no light, apart from the booth lighting; and, in general, they prefer automated inspection. Japanese inspectors tend to have high expectations and requirements for cosmetic defects.

All in all, the meeting proved a success! The presentations were insightful and the discussion engaging.

References

1. U.S. Pharmacopeial Convention. General Chapter <1790> Visual Inspection of Injections. In *USP 41-NF 36*, USP: Rockville, Md., 2018. www.usp.org.
2. U.S. Pharmacopeial Convention. General Chapter <788> Particulate Matter in Injections. In *USP 41–NF 36*, USP: Rockville, Md., 2018. www.usp.org
3. Parenteral Drug Association. *Technical Report No. 79: Particulate Matter Control in Difficult-to-Inspect Parenterals*; PDA: Bethesda, Md., 2018.

PDA Who's Who

John Shabushnig, PhD, Principal Consultant, Insight Pharma Consulting

Guest Editorial: Expect Drug Shortages to Get Worse continued from page 10

5. Invest in advanced manufacturing.

Have you ever wondered why high-priced medications don't experience many drug shortages? Do you want to know why? Biotech companies can afford to and have implemented most of the initiatives above.

The solutions to drug shortages will not be easy and will take hard work, behavioral changes and persistence. The effort is clearly worth the result. Our loved ones, friends and colleagues depend on our success.

As pharmaceutical professionals, we must say, "enough is enough" and demand that everyone who impacts the pharmaceutical supply chain change their approach. That includes congressional leaders, policy makers and experts, pharmaceutical executives, purchasers, healthcare executives, health care providers, payors and consumers. If we do not change, we do not have the right to complain about the results (shortages) of the system we had a part in building.

Today, there is no way a company can sustain itself selling an essential sterile injectable medication for less than a dollar!

Reference

1. Herper, M. and Branswell, H. "Shortage of crucial chemicals creates new obstacle to U.S. coronavirus testing." STAT News. (March 10, 2020) https://www.statnews.com/2020/03/10/shortage-crucial-chemicals-us-coronavirus-testing/

pda.org/2020diworkshop

2020 PDA Data Integrity

WEBINAR SERIES

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The 2020 PDA Data Integrity Workshop is going Virtual!

PDA is bringing back one of its most popular Workshops, as a four-part Webinar Series. The ***2020 PDA Data Integrity Webinar Series*** will explore the latest information and best practices on this important topic, focusing on two of the most crucial pieces of a successful data integrity program: **regulation** and **innovation**.

Learn from leading technology experts and global regulators how you can pivot your company's data governance program from reactive to proactive. This Webinar Series is designed to provide data integrity newcomers and professionals alike with the practical knowledge needed to develop a modern, agile data governance program.

To learn more, visit *pda.org/2020diworkshop*

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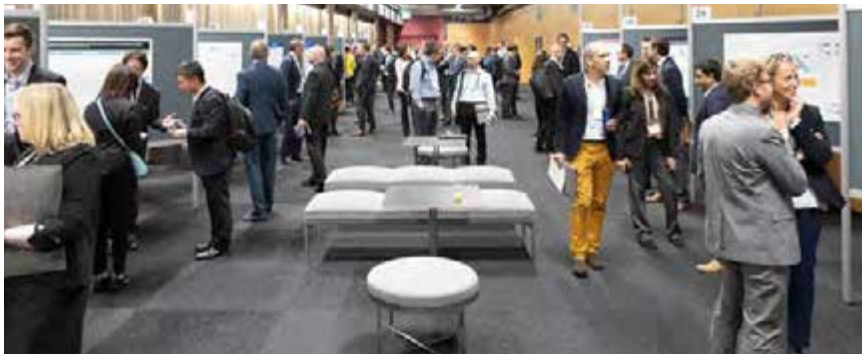
Dennis Lee, Gates Foundation



(l-r) Falk Klar, PhD, PDA Europe; Brigitte Reutter-Haerle, Vetter

(l-r) William Dierick, Terumo; Yoshifumi Torii, Fujifilm Kyowa Kirin Biologics Co.; Philipp Hoerner, Bausch + Stroebel; Liang Fang, WEST

Members of the planning committee behind the conference and exhibition pose for a group photo at the conclusion of the event

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PDA EUROPE VIRTUAL EVENTS

CMO Works Around the Clock to Produce COVID-19 Meds

Rebecca Stauffer, PDA

Recently, three clients of contract manufacturer Berkshire Sterile Manufacturing (BSM) had a special request for the CMO. Could BSM manufacture three sterile drugs that would serve as treatments for COVID-19? And, instead of the normal three- to six-month turnaround time, could they do it in four weeks?

BSM responded immediately. The staff worked long hours and volunteered overtime on weekends to meet the four-week deadline and make these essential medicines available as quickly as possible.

PDA interviewed BSM CEO **Shawn Kinney,** PhD, about how the company answered the call.

Berkshire Sterile staff fill one of the sterile COVID-19 treatments into vials

PDA Letter: Are the drugs aseptically filled or terminally sterilized?

Kinney: All of the COVID-19 drugs that we are working on are sterile filtered and aseptically filled.

PDA Letter: Are any of them biologics? If so, do they require lyophilization?

Kinney: Two of the drugs are biologics but they are not being lyophilized. At this point, BSM does not believe that the clients are interested in long-term stability as much as quick delivery to the clinic to demonstrate efficacy.

PDA Letter: Can you give us an idea of how the filling area is arranged? Are you using isolators or a restricted access barrier system (RABS) or a combination?

Kinney: All of the filling is accomplished in isolators. RABS are used to protect mouseholes leading into and out of the isolators. We have two isolator lines, one manual line and one semi-automated line. A robotic isolator system is in progress but will not be operational until late 2021.

PDA Letter: How do you ensure stability of these products in such a short period?

Kinney: BSM is not performing stability studies for these clients. If stability is being performed, it is being performed by the client or by a contract lab. The client is so focused on getting as much product to the clinic as possible that stability may be determined later.

PDA Letter: Since BSM is making and filling three different products, what sort of cross- contamination measures are you following, e.g., disposables, separate dedicated lines, etc.?

Kinney: All of the COVID-19 drugs are being produced using disposable technologies for all product contact equipment. They are filled in isolators with new sterile gloves every run. Isolators are cleaned after every run and sanitized to a validated 6-log reduction before every run.

PDA Letter: Is BSM also manufacturing other, non-COVID-19 drugs? If so, how does manufacturing ensure that production of these medicines is not disrupted?

How Do These Products Treat COVID-19?

Drug Product 1

This product disrupts a protein in the inflammation pathway to prevent inflammation in the lungs and prevent patients from needing ventilators. This product was filled March 20 with a scheduled release date of April 10. Another batch of this drug will be filled on April 12.

Drug Product 2

This product is an immune-system booster expected to help a patient fight the virus. It is produced through a two-part fill on April 3 and 8.

Drug Product 3

This product comes in two forms (long-lasting or short-lasting) and increases oxygen uptake in the lungs by improving oxygen permeability in the lungs. The long-lasting form is a liposomal product. Each form was filled on April 4.

*Information courtesy of **Sarah Kinney,** Quality Control Associate (Analytical) at Berkshire Sterile Manufacturing.*

Quality is always foremost in our mind. QA keeps up with the review of testing results and documents as soon as they are available

Kinney: At this point in time, BSM has been able to add overtime and weekend work and utilize overflow days to fit in COVID drugs without impacting existing clients.

PDA Letter: What kinds of technologies does BSM use to ensure both high quality and quick release for these very critical drugs?

Kinney: Release testing is performed by traditional QC methods and sterility testing is outsourced. We coordinate with the sterility lab for testing. The lab is very understanding of the importance of COVID-19 drugs and puts the samples on test immediately. We rush the internal testing with overtime if necessary. Quality is always foremost in our mind. QA keeps up with the review of testing results and documents as soon as they are available.

PDA Letter: Is the company using rapid-sterility testing? If not, is the company considering it?

Kinney: BSM is not using rapid-sterility testing at this time. The validation of the rapid test is time-consuming and, right now, we are focused on rapid delivery of as many units as possible. Until the products are demonstrated to be efficacious, there is no reason to consider validating rapid test methods.

PDA Letter: Since these are existing clients, has this changed how Berkshire works with the U.S. FDA and other regulatory agencies in this initiative?

Kinney: BSM has had two successful pre-approval inspections in the past two years. Our clients own the drug products and regulatory filings with the FDA. BSM is prepared to provide any support necessary and welcomes any FDA inquiries, inspections or other actions to get rapid approval of these drugs if they are efficacious.

About the Author

Shawn Kinney, PhD, is President, CEO and one of the co-founders of Berkshire Sterile Manufacturing, Inc., a CMO located in Lee, Mass. He has been involved in sterile fill finish for more than 20 years, implementing and adopting new technologies. In addition, he spoke at the Nov. 13 PDA New England Chapter dinner meeting.

Visual Inspection Practices of Cleaned Equipment: Part I

Walid El Azab, STERIS, and Stephane Cousin, GSK Vaccines

Regulatory and compendial guidelines require that manufacturers confirm process equipment is visually clean following a cleaning operation. Recently, an industry survey showed that visual inspection practices for cleaned equipment differ among manufacturers. At the same time, the survey indicated that while practices and even terminology may differ, this can be accepted by regulators provided processes are well documented.

First, a word about terminology. Many regulatory guidelines and industry technical documents use different terms to describe the step confirming process equipment is visually clean after cleaning. For the purposes of this article, the authors use the term "visual inspection." Other common terms for this step are "visual check" or "visual examination." Note that in this case, "visual inspection" does not refer to visibly checking finished product for particles.

For the survey, 39 responded, representing many European pharmaceutical and biopharmaceutical companies (27 companies in 34 different sites). The manufacturers who completed the survey were: 54% non-sterile (e.g., tablet, liquid, combined product), 13% sterile (e.g., biotechnology, liquid, and lyophilized product), 26% vaccine, 5% medical device, 2% other (e.g., early clinical production).

The European Annex 15 states that "A visual check for cleaning is an important part of the acceptance criteria for cleaning validation" ***(1).*** Visual inspection is a critical step to confirm the effectiveness of cleaning process equipment after cleaning. The acceptance criteria for visual inspection is visually clean. The visual inspection should include direct and indirect product contact surfaces, and requires the equipment surfaces to be visible. When this is not the case, dismantling the equipment to gain access, or using tools such as mirrors, light sources, or borescopes may be required ***(2, 3).*** Modern technology such as digital cameras capable of assessing the surface may also be explored for large-volume vessels, when a visual inspection is challenging.

Visually clean is the minimum standard expected. An additional acceptance criterion, such as the health-based limit, however, is enforced ***(1-5).*** Therefore, a validated analytical method with a sensitivity below the cleaning limit should be periodically coupled with a visual inspection. When applying only visual inspection to determine the cleanliness of equipment, the threshold at which the product is readily visible as a residue should be established ***(3, 6).***

The visual inspection is always performed (to whatever degree possible) at the end of a complete cleaning cycle ***(7).*** The visual inspection is an active and qualitative observation of product contact surfaces to confirm the absence of residue and the next batch production can start ***(7).*** ICH Q7: *Practice Guidance for Active Pharmaceutical Ingredients* states that: "12.76 … Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis."

Photo courtesy of Steris

Back to the survey, 54% of respondents are performing a visual inspection of the equipment surface when it is dry **(Figure 1)**.

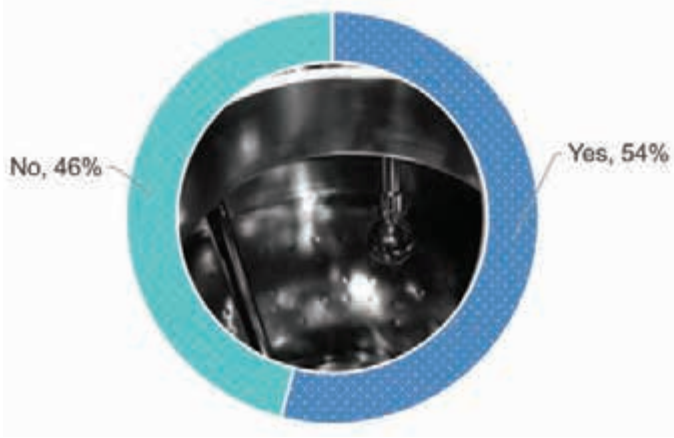

Figure 1 Does your company procedure require you to visually inspect the process equipment surface after a cleaning operation when the surface is dry?

Operators performing visual inspection require specific training because what one can visually see varies

Some technical industry documents suggest that visual inspection should be performed on a dried surface, when possible, to avoid false-negative results ***(8,9)***:

- Active Pharmaceutical Ingredients Committee Guidance ***(10):***
  - "After cleaning procedures are performed, equipment should be dried to allow the visual inspection."
  - "The acceptance criteria for equipment cleaning should be based on visually clean in dry conditions and an analytical limit."

- *PDA Technical Report No. 29: Points to Consider for Cleaning Validation* ***(9):***
  - "Ordinarily surfaces that are visually examined should be dry, as this represents a worst-case condition for visual inspection."

It is commonly known that for some residues, visually clean may only be achieved when the surface is wet, while this is no longer the case when the surface dries.

Equipment design and cleaning cycle parameters may conduct to dry the equipment surfaces, such as having the piping sloped toward the drain, being self-drainable, and the final rinse performed at high temperatures. In some cases, clean air blown into the equipment and the distribution system may help to achieve dryness on surfaces ***(9).***

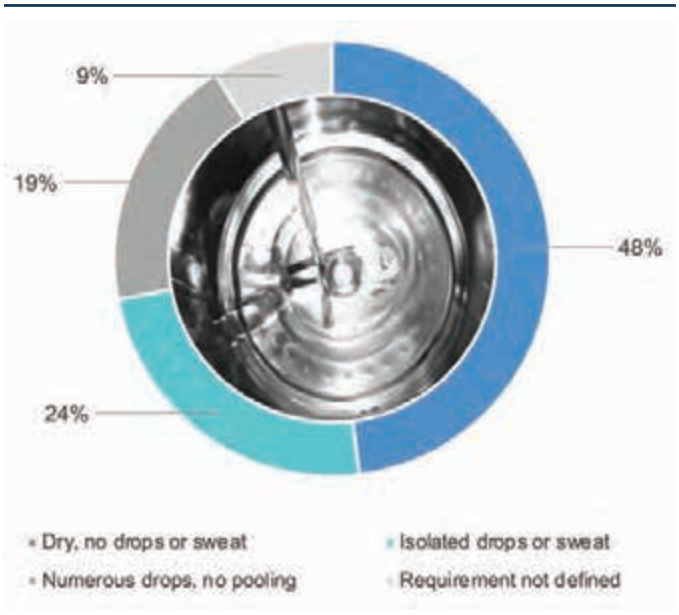

Figure 2 What is the dryness requirement for process equipment following the cleaning cycle is finished?

Despite these parameters listed above being met, however, droplets or moisture ("sweat") on the surface could potentially be observed and may be acceptable if adequately justified.

As **Figure 1** shows, 48% out of 54% who responded "yes," when asked if they visually inspect equipment surfaces when entirely dry **(Figure 2)**. 24% out of the 54% allow some partial wetness (e.g., isolated drops or sweat) of the surfaces during a visual inspection of the cleaned equipment (**Figure 2**). 19% out of the 54% accept numerous drops but no pooling of water. 9% out of the 54% have not defined the dryness requirements.

Different levels of dryness are acceptable if adequately justified and backed up by data demonstrating the absence of impact on the visual inspection post-cleaning and bioburden proliferation during clean storage, e.g., robust instruction and training using photos to avoid deviation. Finally, none of the 54% of the manufacturers that visually inspect their equipment when the surfaces are dry authorize for standing or pooling water on the equipment surfaces, as suggested in the U.S. FDA inspections guide ***(10):*** "…For example, equipment should be dried before storage, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations."

Considerable responsibility is given to an operator to decide whether equipment surfaces are visually clean. Therefore, the operators should be able to inspect all surfaces of the equipment visually. If not possible, adequate or advanced tools should be available to guarantee proper decision making ***(2, 3, 9, 11).*** A visual inspection of a large vessel through a sight glass is restrictive due to hidden surface. EMA suggests that the ability to visually inspect the equipment, such as distances observed in the field, should be taken into consideration in a Q&A document ***(3),*** recommending that "written instructions specifying all areas requiring visual inspection should be in place and records clearly confirm that all inspections are completed." Finally, detailed procedures and training on visually clean criteria are mandatory to ensure correct decision making. The level of training and qualification to visually inspect should be commensurate by the risk of cross-contamination ***(3, 7, 9, 11).***

When it comes to photos, 38% of the respondent surveyed have defined visually clean criteria by also adding photos and examples of clean status **(Figure 3)**. 46% rely on the operator's understanding of visually clean, coupled with a theoretical definition of visually clean in the procedure. Finally, 16% (3% and 13%) rely on the operator's experience and training (using specific support ➤

visually clean criteria seem to vary among European manufacturers

or pictures) of a visually clean surface **(Figure 3)**.

Operators performing visual inspection require specific training because what one can visually see varies with the distance, angle, lighting, the nature of the surface, the dryness level and the inspector's visual acuity ***(3, 7, 9).*** EMA suggests that eyesight testing (or visual acuity) should be performed periodically, and the competency of the operator should be proven through a practical assessment ***(3).*** The ISPE Risk Mapp suggests that: "In situations where the method of detection is visual only, it is important to understand the visual acuity of the staff, and what level of residue is considered safe ***(7).*** If the safe level is below the visual acuity of the staff then the risk of failure not being detected may be considered high whereas if the safe level is well above (several orders of magnitude), the visual acuity of the staff the risk of failure not being detected may be considered low."

The frequency of visual acuity test and visual acuity limit would depend on specific variable such as the:

- distance between the inspector and the inspected equipment surface ***(3, 7, 12)***
- equipment configuration and surface nature ***(7,8)***
- surrounding lighting conditions ***(3, 7, 9, 12)***
- frequency of analytical testing ***(3, 7-9, 11,12)***
- residues toxicity, cleaning limit versus visual detection limit ***(3,6,7)***
- visual inspection only is performed to confirm the cleanliness of an equipment ***(7)***

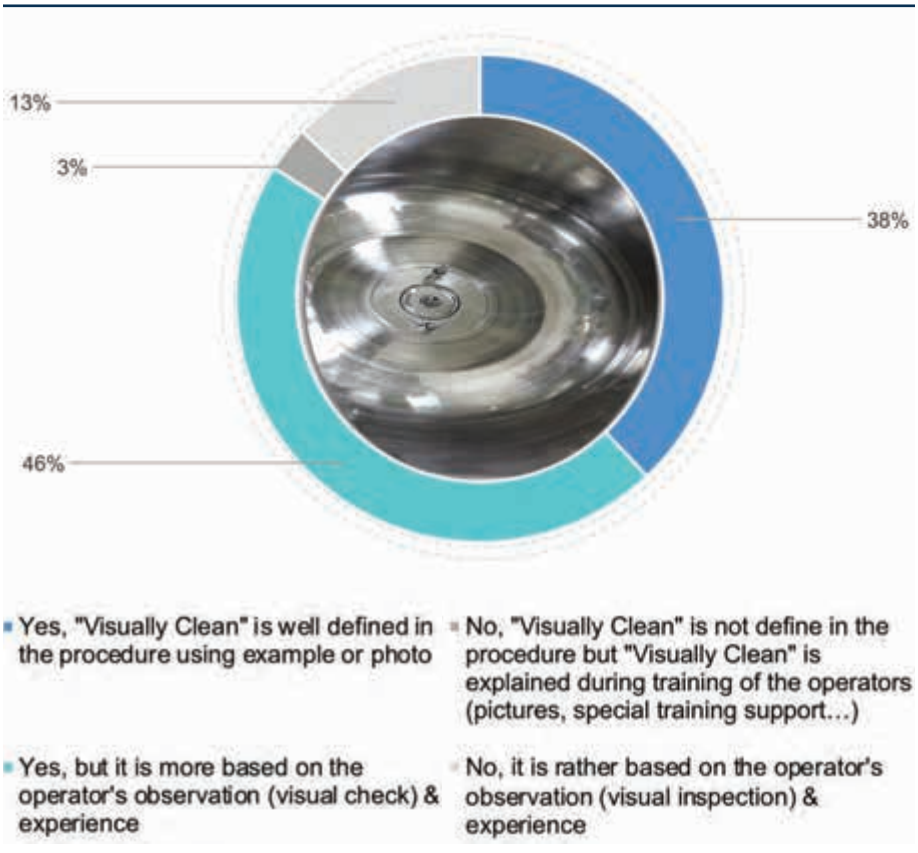

Figure 3 Does your company define and detail the meaning of "visually clean" criteria?

38% of the respondents do not require an operator's certification or qualification **(Figure 4)**. Yet 49% train their operators to visually clean on the field (in front of the equipment). Finally, 13 % qualify their operators.

Some manufacturers have defined the visual residue limit, using coupons, an operator could detect ***(13, 14).*** Also, some of them mimicked the distance between the operator and the surfaces to be inspected on process equipment ***(15, 16).*** When the visual residue limit is lower than the cleaning limit visual inspection alone as an acceptance criterion may be enough ***(7).***

Does a certification or qualification along with a training program ensure operators' competency to inspect a surface visually? Following the precept of ICH Q9: *Quality Risk Management* ***(17),*** the answer would generally depend on the:

- number of historical visual inspection deviation due to operator training
- difficulty in inspecting the equipment (equipment configuration and background environment such as lighting, angle, etc.) ***(3, 7–9, 11, 12, 18, 19)***
- type of visual inspection being used; qualitative or quantitative visual inspection ***(7,12, 13–16, 18,19)***
- visual inspection is not supplemented with analytical testing ***(13–16,18)***
- frequency of analytical testing performed with visual inspection
- analytical method sensibility against the cleaning limit, toxicity (based on the health-based exposure limit) of the residues ***(1–7, 9,11)***
- presence of a double-check

Conclusion

The visual inspection concept and "visually clean" criteria seem to vary among European manufacturers based on their experience with the cleaning process execution and understanding of the regulatory requirements. The visually clean criteria, however, must be clearly defined in the procedures. Operators performing visual inspection require specific training, which can be based on their own experiences. ➤

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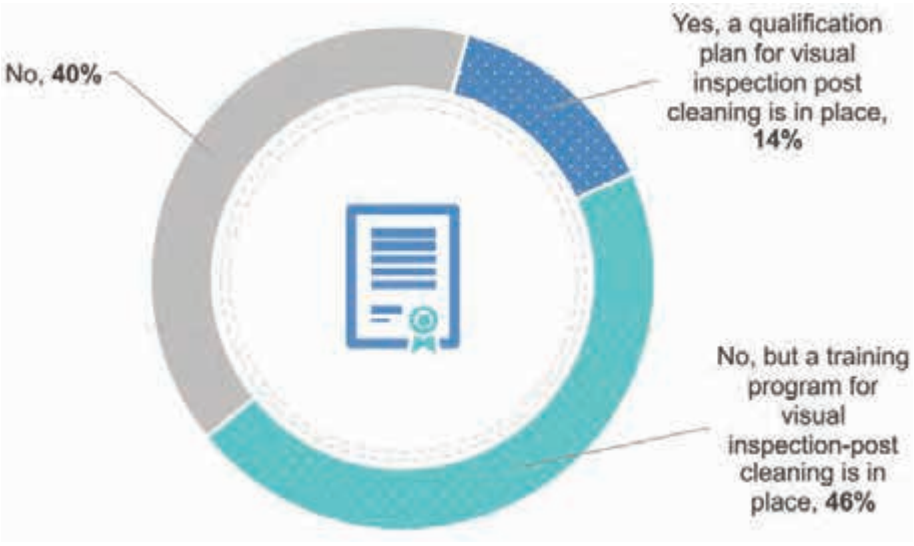

Figure 4 Does your company have a certification or qualification program in place for visual inspection?

The variability in practices between manufacturers, as suggested by the survey results, may be acceptable when the risk is documented. Following the precepts of ICH Q9, the level of effort and formality should be commensurate with the patient's risk.

In Part II, a case study and suggested minimal requirement for visual inspection of cleaned surfaces will be presented. **[Editor's Note:** Part II can be accessed on the *PDA Letter* website**.]**

Author note: We wish to sincerely thank all those who participated in the survey.

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The PQL Team Part III: Staying Ahead

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

[Editor's Note: Parts I and II of this series on AstraZeneca's Product Quality Leader (PQL) program can be read on the *PDA Letter* website**.]**

The PQL role is established, a team of PQLs built, and a capability/skills matrix developed to help the PQLs succeed and grow. The next step involves expanding their skillsets by applying additional lean concepts that will move PQLs toward continuous improvement and "staying ahead."

A Gemba Walk is one lean tool used to improve and standardize the critical review processes, the use of which has resulted in more efficient and reliable review outcomes.

First, what is a Gemba Walk? "Gemba" or "Genba" stems from the Japanese phrase *Genchi Genbutsu,* meaning "the actual place," the location where the work occurs. A concept developed by Toyota, a Gemba Walk takes leaders to the heart of the operations bearing a sense of curiosity. They ask questions about processes. They listen and observe. And, in doing so, they find opportunities to support their staff in solving problems. Hence, the Toyota mantra: "go see, ask why, show respect."

A Gemba Walk is one of the basic tenets of lean management, yet it can be challenging to set up for the quality review function. The department responsible for quality usually does not own, nor is it accountable for, the relevant process or function. Typically, it serves the role of arbiter whose primary objective is to protect and safeguard the patient by assuring compliance with regulations and/or standard procedures.

The team that developed the PQL role at Astra Zeneca recognized that it made more sense to limit the scope of the Gemba Walk solely to the PQL review function. The specification review process was selected because it was deemed critical from the completed PQL capability/skill assessment (see Part II). A Gemba Walk designed for the PQL review process of a typical drug substance/product specification revision is illustrated in **Figure 1**.

The specification review was a new and intense PQL review task and, overall, a new experience for most PQLs. It examines a critical quality element with potential patient and business impact, which can be revised or reviewed at multiple lifecycle stages for each product. Thus, the criticality of the need to standardize this specific task ranked higher than all other PQL review tasks.

The Gemba Walk was performed by a team, comprising dedicated lean coach and an observer with a high degree of expertise with this review task. This ensured the accuracy and thoroughness of the first review case study. Assessing an actual PQL review process "live," instead of using a retrospective simulation, was critical to the outcome. The PQL involved was fully trained to execute this critical review process but was not highly proficient at this point, it being a relatively new task.

The PQL had the following documents available at the time of the actual interview:

- AstraZeneca Specification Setting Guidance
- AstraZeneca Standard Procedure for Specifications
- Relevant Justification of Specifications (JOS) form attachments, such as specification committee meeting minutes
- Existing informal "Job Aids," including a description of the review process steps

Process flow maps for a high-level specification revision and an initial (detailed) PQL review (neither of which were used in this Gemba Walk)

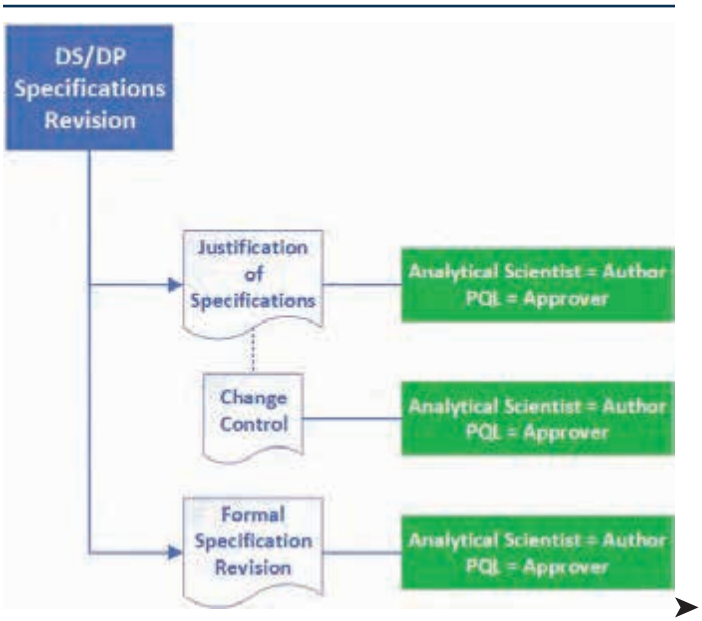

Figure 1 Gemba Walk "Scope" for PQL Specification Revision Review

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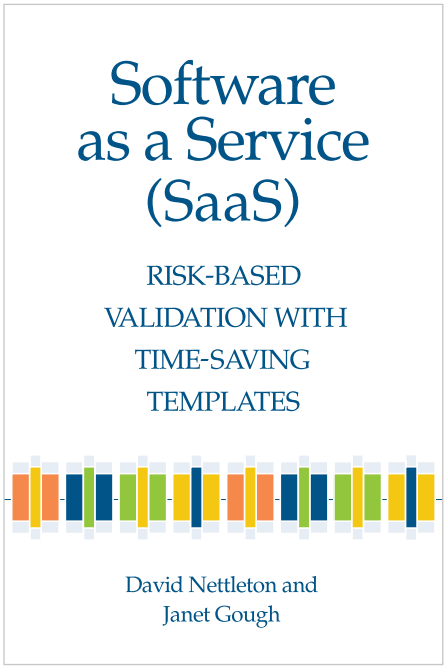

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Figure 2 (Simplified) Example of a Post-Gemba Job Aid for a PQL Review Task

Clinical Master Specification Review Job Aid

Description:
This guide provides information on how to review AZ Biologics clinical master specifications.

Originator: Analytical

Source Systems: AZDoc

References (in addition to training):
- Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products

Documents for review:
- Justification of Specification (JOS)
- Specification Change Control Form
- Master Specification (MS) for Investigational Medicinal Product
- Current Effective Master Specification (for revisions)
- Control Strategy Specification Committee (CSSC) Meeting Minutes

Decision Maker(s): CSSC

Advisor(s): CMC

Informed: BPD

Training Required? Yes
- Standard Procedure for Change Management for Master Specification
- Guidance for Specification Setting for Clinical Products
- Standard Procedure for Preparation of Master Specification for Investigational Medicinal Product
- Preparation of Master Specifications for Commercial Products

SME(s): CSSC, PQL Team Leader

PQL Review Guide:

When reviewing NEW Master Specifications (MS):
- Ensure *Part Number, Product Name, Specification Number* and other JOS *SECTION 1: General Information* are consistent across: JOS, MS, CSSC minutes/approvals.
- Ensure *Test, Method (DLIMS Test Analysis),* and *Acceptance Criteria* are consistent across: JOS, MS, CSSC minutes/approvals.
- Stability data generated in the PFS-SA configuration

CSSC not required for platform phase I/II
- If CSSC minutes are not available contact Stephan Krause (or current CSSC secretary) to assure CSSC presentation was not required
- Ensure all *Justifications of Specifications* exist and are complete on JOS form
- Ensure all required reviewers/approvers are on the review panel
- Ensure Endotoxin calculations are included and accurate
- Ensure all storage condition part numbers are listed and accurate

When Reviewing Master Specification REVISIONS
- Ensure version history indicates what is changing and references the change control form in AZ Doc
- Ensure CSSC has approved the change, if required
- Ensure change control form aligns with change and clearly identifies any potential gaps/risks
- Ensure spec aligns to the changes in the change control form
- Ensure RA and AQL are on the review panel
- Ensure Section III responses contain justifications (as applicable)

Figure 3 Gemba Walk Outcomes and Benefits for PQL Team and Partners, Customers and Stakeholders

For Product Quality Team	For Stakeholders/Customers
More useable master specification review job aid	Faster approvals
More consistent and focused review process	Fewer documentation errors
Fewer review cycles (right the first time)	More suitable and defendable JOS/Change Control form content

All documents and information were reviewed from electronic records. The review focused primarily on the JOS form. Because it includes all specification revision information and the relevant content is transcribed unchanged into the master specification form, the JOS form is the main stage of the specification revision process.

A Gemba Walk tracker was used to capture challenges, gaps, or opportunities identified that would achieve a more standardized first-time, complete review cycle. The tracker also included improvement actions which were managed with standard project management tools. At that point, the team of PQLs was fully prepared to present the planned PQL review process improvements to the process owner and other involved parties. By approaching partners in other departments with an emphasis on their benefits, the PQL hoped to more readily obtain their support for suggested changes outside the PQL review.

As a result of the review, the process flow maps for the entire specification process were revised, standard procedures were updated as necessary and a new job aid was written specifically for the PQL review process. An abbreviated version of the new job aid is shown in **Figure 2**. Any lessons learned from future reviews will be reflected in periodic job aid updates.

The results and benefits of this focused Gemba Walk for a PQL review task is summarized in **Figure 3**.

Throughout all stages of the PQL process, from design to building skills to advancement, most of the feedback from those involved has been positive. Testimonials noted that adding the PQL role has enabled processes to be more flexible while allowing all the pieces of the process to be viewed both individually and as a whole. Because the PQL provides an objective view of a process, there is no fear of voicing concern if a process is unclear or inappropriate. This role has enabled the company to assure that best practices are engaged, ensuring the products that reach the market are safe, effective and available for the patient.

[Editor's Note: See online article for author biographies and headshot photos**.]**

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16 **LIVE eLEARNING** PDA 716 Bio/Pharmaceutical Filtration Process Validation | *pda.org/2020virtualedu*

16-18 **LIVE eLEARNING** PDA 808.3 Characteristics of Pharmaceutical Elastomers and Aluminum Seals in Parenteral Packaging Systems | *pda.org/2020virtualedu*

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4 Ways to Manage Your Supply Chain

Dawn MacNeill, MilliporeSigma

Drug shortages, a topic which roared into headlines in 2011 and has since remained an important concern for industry.

The number of new shortages in the United States peaked at 267 in 2011. In response to this crisis and other supply chain concerns, global regulators released several guidances addressing the issue, including the 2011 EU Falsified Medicine Directive, the 2012 U.S. Food and Drug Administration (FDA) Safety and Innovation Act and the 2013 U.S. Drug Quality and Security Act.

While the incidence of drug shortages has generally declined since then, a recent uptick— unrelated to COVID-19—has surfaced in the United States and Europe ***(1,2).*** As a result, this continues to be an area of intense focus for the biopharma industry, their suppliers, regulatory agencies and, of course, patients. A 2019 FDA report that detailed potential solutions to the issue of drug shortages cited logistical challenges as one of the causes of the issue ***(3).*** With rapid growth, biopharmaceutical manufacturers are increasing their capacity throughout the globe and leveraging contract manufacturing sites. Thus, supply chains have become longer and more complex – making it more challenging to mitigate supply chain risks.

Given the central role of supply chains, more effective management can help minimize the risk of drug shortages. While risk is inevitable and increasing in today's climate, it all comes down to proactively identifying and managing that risk. And suppliers must be more actively engaged in mitigating the risk of supply disruptions, enhancing visibility and traceability, and enabling process predictability and control. Here are four strategies for ensuring effective supply chain management between manufacturers and suppliers.

1. Share Information and Anticipate Demand

To help secure the supply of life-savings drugs, the relationship between biopharmaceutical manufacturers and key suppliers must evolve into a trusted and transparent strategic partnership. Information, data and ideas need to flow freely throughout a patient-centric supply chain. Biopharmaceutical manufacturers should engage suppliers in their supply chain risk mitigation process, from both supply and product quality perspectives. This can be accomplished, in part, by sharing basic information with suppliers about the chemicals and consumables specified in manufacturing processes, batch requirements and production schedules. If bills-of-material are used to manufacture a drug on the WHO List of Essential Medicines or a drug for cancer, for example, the chemicals and consumables could be deemed critical by the supplier and result in more robust risk mitigation. This knowledge could influence the supplier's supply-chain activities, such as forecasting, safety stock inventory planning and dual-sourcing, capacity planning and evaluating high-risk geo-political areas. It may also help the supplier prioritize and allocate activities in the unfortunate event of capacity constraints.

Similarly, sharing information related to critical process parameters and unit operation results could improve quality control and reduce raw material variability. This, in turn, can enhance process characteriza- ➤

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tion and control and enable a more mature quality management system. Ultimately, the action of sharing information can support biopharmaceutical manufacturers in their pursuit of a competitive quality rating.

Generally, suppliers understand that demand will never be 100% accurate or predictable. Yet, if manufacturers were willing to share strategic information affecting their demand-planning — planned inventory strategy changes, terminal buys of pre-change material and such risk mitigation activities as dual-sourcing and large capacity investments, as well as the confidence levels related to their demands — the impact on the overall supply experience and key performance metrics would invariably be positive.

2. Build Relationships

The benefits of a partnership interchange between manufacturer and supplier, where direct and frequent exchanges take place at a strategic, rather than operational and transactional, level can be significant. This dialogue is most effective when manufacturers are willing to share information about their molecules and raw materials and their intended use as well as detailed batch requirements. If the supplier understands the bill of materials, it can identify what the expectation will be on demands. In this situation, proactive and transparent communication allows the collective team to course-correct before a minor incident becomes a major issue. At the end of the day, the goal is to deliver materials to the customer and medicine to the patient. If a supplier does not have the infrastructure in place to handle significant changes in demand, it could open a door to idle biopharmaceutical manufacturing capacity, potential drug shortages and financial losses.

Biopharmaceutical manufacturers should also be prepared to accept an increase in change notifications as suppliers expand their own supply networks, increase capacity and qualify secondary sources. Manufacturers also should prepare to accelerate the acceptance of changes. At the same time, suppliers should follow a robust change management process in alignment with industry best practice guidances. They should provide comprehensive data packages to support customers in accelerating the acceptance of these changes, including acceptance of finished goods from new plants or with second sources of raw materials.

3. Ensure Business Continuity

Perhaps the most important element of supply chain risk management is a robust business continuity strategy, one that seeks to identify, assess, quantify and develop risk mitigation measures.

As part of a business continuity planning process, several dimensions across the supply chain should be examined: raw materials, capacity vs. demand, IT infrastructure and distribution network. A heat map of probability and impact can be used to identify the greatest risks and potential actions to mitigate those risks. In some cases, the solution might be investing in new equipment or a new production facility, ; the adoption and qualification of dual raw material sources or suppliers.

> **Suppliers to the biopharmaceutical industry are implementing strategies to ensure that their supply chains are more robust and resilient**

Biopharmaceutical manufacturers should map their suppliers; manufacturing sites to know where single-use components and raw materials are actually manufactured. This activity would enable biopharmaceutical manufacturers to take proactive steps in the event of a hurricane, such as prepositioning inventory to avoid stock outs.

4. Apply Consumerization

The principles of consumerization, leveraged successfully in other industries, can also be used to improve the biopharmaceutical supply chain and customer experience in terms of procurement, quality, regulation, operations and logistics. PricewaterhouseCoopers defines consumerization as "the acknowledgement of the growing role of consumers and the need to develop strategies and market offerings that fulfill their needs and preferences and fully engage them in an end-to-end customer experience" ***(4).***

In a world where consumerization has gone from a trend to an expectation, it pays to draw inspiration from Amazon, Domino's, Uber and Netflix. These companies in mature industries attribute a good part of their success to providing consumers with a user-friendly digital experiences to differentiate themselves. Their goal is maintaining product quality and supply reliability while simultaneously making it easier for consumers to do business with them.

The principles of consumerization outlined above can be leveraged to improve biopharma industry supply chains and include:

- Real-time visibility of order and shipment information
- Availability and transparency of data to qualify products being ordered and used
- Electronic transfer of product quality information, such as certificates of analysis, certificates of quality and genealogies
- Use of web-based tools to map suppliers and anticipate possible stockouts due to natural disasters and pandemics

Conclusion

Everyone can agree that one drug shortage is one too many and, as an industry, we need to direct our attention to reducing this number to zero. Suppliers to the biopharmaceutical industry are implementing strategies to ensure that their supply chains are more robust and resilient, but they cannot do it alone. Closer collaboration with the industry, along with increased trust among stakeholders and shared information about critical raw material needs—both now and forecasted for the future—will certainly help. In addition, the accelerated adoption and implementation of digital technologies, enabling and facilitating the exchange of data between suppliers and biopharmaceutical manufacturers, will transform how we do business together.

Clearly, everyone in the supply chain needs to work together to solve one of the toughest challenges in life sciences. The accelerated implementation of innovative supply chain strategies will be a major step towards mitigating the risk and number of drug shortages.

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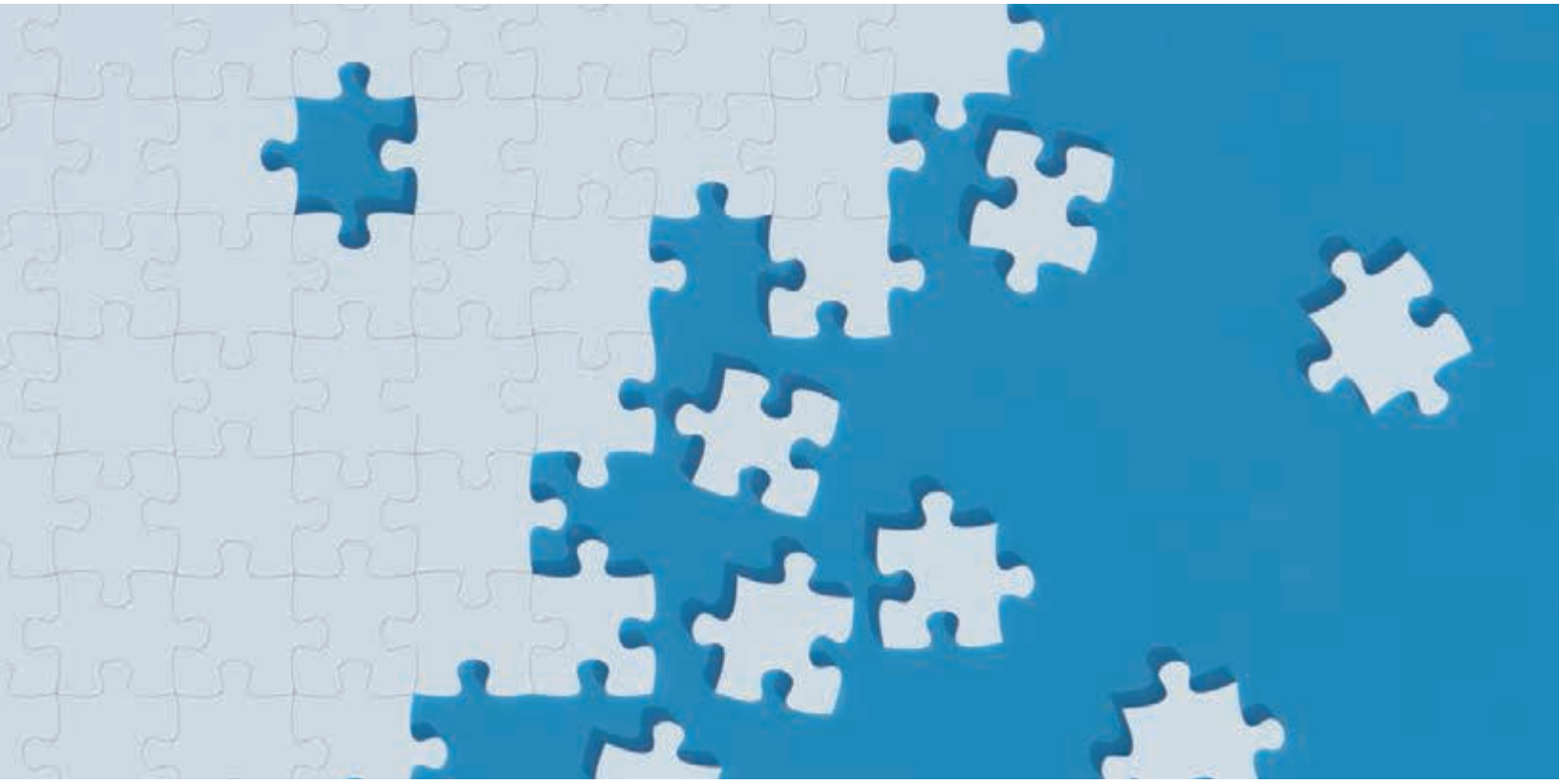
About the Author

Dawn MacNeill is Head of Supply Robustness, Process Solutions, at MilliporeSigma.

PDA Members Recommend ICH Q9 Changes

Hal Baseman, ValSource



At PDA's *Risk Management in the Regulatory Landscape Conference* held in Washington, D.C., **Stephan Roenninger,** PhD, Director International Quality External Affairs, Amgen, announced ICH's intent to revise parts of the ICH Q9: *Quality Risk Management* (QRM) guideline ***(1)***. PDA provided an opportunity for attendees to suggest changes to the guideline during a facilitated roundtable discussion at lunch on December 10**.**

A sampling of the changes recommended was discussed that afternoon in a panel session featuring Roenninger, **Greg Claycamp,** PhD, Biologist, U.S. FDA, and **Martin Nemec,** PhD, Senior Biologist/Evaluator, Health Canada. **Hal Baseman,** COO, ValSource, and **Steven Mendivil,** Consultant, moderated. PDA will share the suggestions captured during the roundtable and panel meeting with its team to inform their outreach to ICH.

Participants demonstrated good insight into the needs of QRM in general and provided sound recommendations for improving ICH Q9. Many of the recommendations and comments expressed common concerns.

Output from the discussion is listed below.

Roundtable Recommendations to ICH

- Align, where applicable, the respective guidance and expectations for pharmaceutical and medical device QRM by comparing, adding relevant elements or merging elements of ICH Q9 with *ISO 14971:2019 Medical devices — Application of risk management* **(2)**
- Merge some principals of risk management guidance for devices into Q9 and add some guidance on combination products Emphasize the importance of outcomes rather than tools and justifications
- Add detail on risk reviews, emphasizing review of the original assessment to ensure that changes or events/deviations have not been missed or have not added risk
- Remove the perception that QRM is not enforced and therefore not part of the quality system
- Consider how QRM fits into, works within and can support the pharmaceutical quality system, promoting recognition by FDA for QRM as a required quality system, emphasizing that QRM is everyone's responsibility within an organization, and showing where QRM and Q9 fit with respect to other ICH quality-related guidelines
- Emphasize the link between QRM and quality systems such as deviation management, CAPA, audit and change control, i.e., a holistic systems approach ➤

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to QRM, rather than an isolated program; plus clarify that QRM extends to support systems, like IT systems

- Promote alignment of QRM compliance expectations between European and U.S. regulators
- Bridge the gap between regulations, SOPs (the what) and integration (the how)
- Offer strategies for reporting QRM compliance
- Provide examples or case studies to illustrate QRM tools and approaches, e.g., examples of communication flow and supply chain-related QRM situations
- Emphasize the importance of QRM in the development space
- Provide guidance on the training and documentation needed for applying QRM and risk elimination
- Provide additional clarification for the purpose and difference between QRM elements and steps, including the difference between risk evaluation and risk control
- Address risk register in the overall QRM program generally, especially in respect to risk communication
- Add a more inclusive glossary of terms, in addition to defining and describing formal vs informal risk assessments; terms and language should be updated to match current usage in the global industry and the guideline should use language that emphasizes how Q9 can help empower a quality culture
- Define roles, particularly those of decision-makers
- Emphasize QRM planning and the use of QRM principles in the planning of activities

PDA is in communication with ICH as the organization plans to change portions of Q9: Quality Risk Management. Updates will be available in future issues of the *PDA Letter.*

In the meantime, one of PDA's recently published technical reports,

PDA Technical Report No. 54-6 (TR 54-6) Formalized Risk Assessment for Excipients, looks at the excipient risk assessment process and is the sixth in PDA's series of quality risk management technical reports. To learn more, visit the PDA Bookstore (www.pda.org/bookstore)

- Provide guidance on the order of precedence, for example, the preference of risk prevention over detection
- Provide guidance on the use of tools and levels of documentation required during different stages in the lifecycle, based on tool and process complexity, including the use of QRM for legacy processes and products
- Provide instructions for performing and explaining tools, such as FMEA
- Provide more guidance on how to determine risk acceptance levels and criteria
- Include guidance on how to define "risk" within certain contexts
- Include guidance on determination and use of risk questions
- Contrast implementation vs maturity metrics
- Consider the correlation between quality and safety risk and risk culture
- Delineate differences between QRM and enterprise risk management; clarify levels of maturity for QRM in enterprise risk management and show examples of QRM success within mergers, acquisitions and changes of leadership
- Encourage companies to define QRM, risk and uncertainty according to their own culture
- Avoid getting stuck in discussions about nomenclature, terminology and classifications
- Provide guidance on determining risk and making decisions where little or no data is available
- Include visuals, such as a workflow, to help illustrate key points
- Ensure revision creates guidance that is forward-looking and considers the state of industry beyond what we are doing today

Thank you to all of the participants, the planning committee and co-Leaders ***Ghada Haddad****, Merck and* ***Susan Schniepp,*** *Consultant; and the roundtable session facilitators;* ***Denyse Baker,*** *AstraZeneca,* ***Eva Urban,*** *CSL Behring,* ***Stacey Largent,*** *Concordia ValSource,* ***Annette Bacchus,*** *PDA,* ***Marcello Colao,*** *GSK Vaccines,* ***Bettine Boltres,*** *West Pharmaceutical Services,* ***Jaap Venema,*** *PhD, U.S. Pharmacopeia, , and* ***Tiffany Baker,*** *Concordia ValSource. Plus, special thanks to* ***Steven Mendivil*** *for helping organize the session.*

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PDA Study Explores Role of A.I. in CPV

Tony Manzano, bigfinite

The complexities associated with drug manufacturing are greatly increased with biopharmaceuticals due to the intrinsic variability of the materials involved and the interconnected processes. The control of these multivariate operations must be managed under advanced statistics capable of interpreting complex reactions with multiple factors. The variety of information to be managed and the need to understand the sensitivity of the biosystems suggest that manufacturing in this area could benefit from artificial intelligence (A.I.).

To learn how A.I. could enhance continued process verification (CPV) for biologics, PDA's Process Validation Interest Group has embarked on an experimental project: CPV of the Future. This project aims to establish a standard procedure for CPV in fermentation operations, applying A.I. as a valid analytical method for process control. This initiative has been designed to explore three distinct phases—Process Design, Continued Process Verification and Process Performance Qualification. The first, Stage 1, focuses on CPV (**Figure 1**).

In Stage 1, the commercial manufacturing process is defined, based on knowledge gained through development and scale-up. Stage 3 requires continuous assessment, based on Stage 1 principles, in order to ensure the validity of the current factors being considered and process understanding.

This PDA initiative comprises a set of experimental studies that will focus on improving production of the recombined protein generated by the fermentation of the *Pichia pastoris* microorganism under different conditions of oxygen supply. Specific attention will be paid to hypoxia settings. Using a bioreactor of five-liter volume, fermentations will be performed that produce batches controlled through automatic and manual operations, measuring the following factors:

- Process parameters (pH, temperature, dissolved CO2, dissolved O2, agitator speed, air flow rate, substrate concentration and ethanol concentration)
- KPI – calculated in the laboratory (growth rate, performance indexes, protein concentration, substrate consumption, O2 consumption, CO2 production, respiratory quotient and carbon emission rates)
- Raw materials
- Room and atmospheric conditions
- Manual operations (settings and sampling information)

The first stage of this study will consist of nearly 20 batches with a specific configuration defined by a design of experiments (DoE). This will provide a set of raw data and calculated variables to determine which could be considered critical factors. The analytical strategy is based on a PCA model where the principal components will be used as variables that feed an A.I.-supervised model. Gradient-boosting regressor and random forest regressor are two A.I. algorithms that will be applied in this experiment due to previous success using them in biologics and molecular research ***(1,2).*** Both algorithms are machine-learning techniques for regression, which will produce a prediction model in the form of an ensemble of weak prediction models configured as decision trees for this experiment. The known critical quality attribute (CQA) values will determine the acceptance of the A.I. mod-

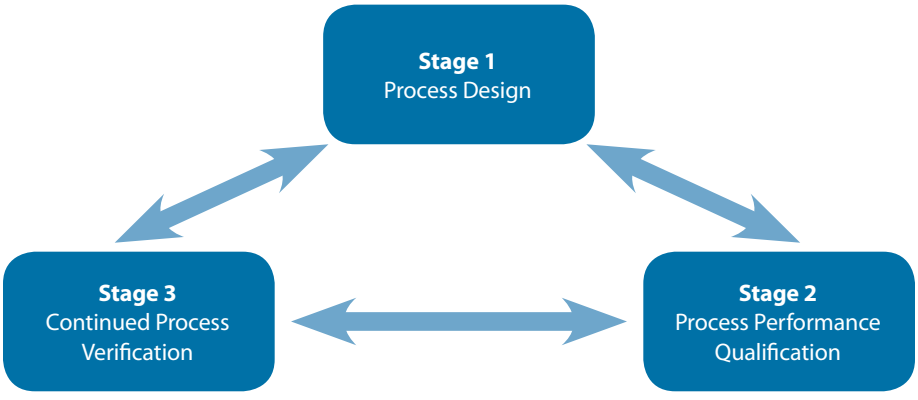

Figure 1 Three Stages of Process Validation

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els during the verification phase, while the continuous process data and environmental records will be used to train the models. From the CPV perspective, considering the principal components with an explanatory percentage higher than 80% as predictor factors in the A.I. models is part of the experiment providing innovative vision. The project also includes the principal components as predicted values in real time as well as the rest of the factors considered critical to characterizing the fermentation process. Therefore, the principal components will be calculated in real time and in the same way as the rest of the process parameters identified as relevant for the fermentation.

Based on the guidelines described above, the CPV of the Future project expects to cover three areas of interest:

Biotechnology: Fermentations will produce batches of biomass brought for *Pichia pastoris* microorganisms. A deeper knowledge of the relevant factors involved in the fermentation of Pichia under hypoxia conditions is expected from this study. Additionally, the inclusion of environment variables and manual operations in the analysis will be considered in order to design subsequent studies for scale-up and technology transfer in larger bioreactors (75 liters to 250 liters).

Technological areas: As an output of this study, a standard procedure will be established that integrates biochemical operations with technologies embraced by Industry 4.0. The Industrial Internet of Things, cloud and serverless infrastructures designed under software-as-a-service architectures, big data aggregation operations and A.I. will drive the electronic information toward so-called "Smart Factory" good practices. A.I. algorithms will be applied using datasets generated by the produced batches in order to obtain A.I. models. The outcome of the proposed A.I. models will focus on various purposes: root cause analysis for batch failures, early detection of wrong batches, critical parameter identification, pattern recognition and critical variables prediction.

Quality control and good practices: Quality control will manage the last tier of the study, based on the continuous process verification concept and the proposal of new standards to apply A.I. as an analytical method in fermentation production. The quality analysis is based on development of a DoE where the critical factors and the A.I. elements are considered in its strategy. Figure 2 illustrates the proposed schema.

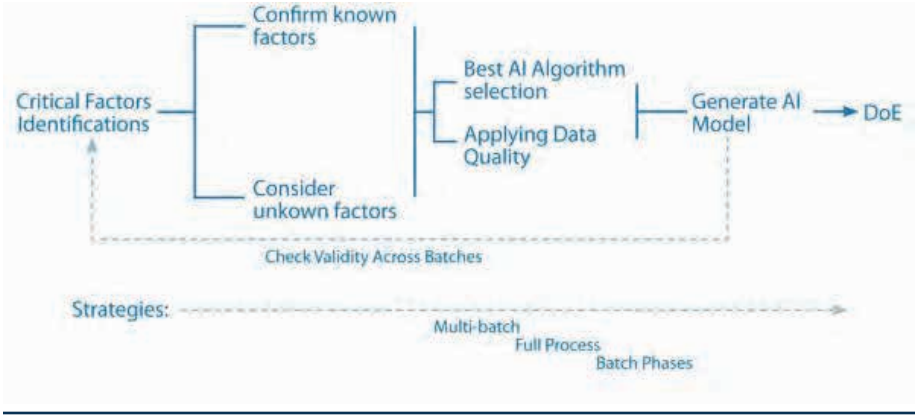

Figure 2 Proposed strategy for the development of a DoE where CPP, CQA, other variables and the A.I. elements needed to comprehend the system are included as factors.

Beyond the presupposed benefits presented by the A.I. application in a CPV context, the described requirements to implement the entire framework boast a new way to understand the fermentation process from a multidisciplinary perspective. This project is the beginning of a journey to determine how A.I. techniques will help manufacturers comprehend the complexity inherent to the pharmaceutical processes. PDA will share the results of the study in the future.

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About the Author

Toni Manzano is Chief Scientist Officer and co-founder of Bigfinite, a company that provides cloud, big data and A.I. services for biotech and pharma companies. He is member of the A.I. Core Team in the A.I. Health, Xavier University of Cincinnati, A.I. and Big Data SME for Science in the Parliament (Madrid), Professor at the Autonomous University of Barcelona and member of the Scientific Committee of PDA Europe.

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PDA Responds to U.S. FDA COVID Guidance

29 May 2020

Dockets Management Food and Drug Administration 5630 Fishers Lane, Rm 1061 Rockville MD 20852

Re: Guidance for Industry: Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products

Dear Madam or Sir:

PDA appreciates the opportunity to comment again on *Guidance for Industry: Planning for the Effects of High Absenteeism to Ensure Availability of Medically Necessary Drug Products* [MNPs] (Docket No. FDA-2009-D-0568). We appreciate your thoughtful review of our prior comments on the draft guidance. We hope that these comments on the revised version of the guidance, informed by recent experience, are helpful.

The guidance provides useful information, and lessons from the current coronavirus emergency may provide pathways for making this guidance even more useful. PDA believes that broader application of the principles in this guidance could help companies better prepare for future emergencies. Similarly, PDA's Technical Report 68 *Risk-Based Approach for Prevention and Management of Drug Shortages* provides guidance and information that can assist in the proactive prevention of drug shortages. FDA may wish to consider referencing this Technical Report in this guidance and in other materials.

First, in the coronavirus pandemic, manufacturing sites have had daily challenges in personnel status, supplier status, transportation options, mitigation protocols, and other factors that impact manufacturing capabilities. As a result, manufacturers are frequently updating emergency plans ("Plans"). In practice, manufacturers have not had a single "detailed Plan designed to maintain adequate supply of MNPs" that "remain[s] active continuously," but an evolving Plan that may look very different week to week and month to month. Returning to normal operations likewise probably will not be a binary yes/no decision, but a fluid and gradual process.

In light of this evolution, PDA suggests that FDA revise section III.F Notifying CDER to allow manufacturers to provide the most relevant information to CDER in a manner that is most useful to and accessible by the Agency. To guide CDER in revising section III.F, we suggest the following:

- Please consider allowing manufacturers to use risk assessment principles to determine the most relevant and impactful information to be submitted to CDER. We would welcome general parameters for the information that CDER seeks, but we believe that CDER would obtain more precise and actionable data if this guidance expressly allowed manufacturers greater flexibility to respond with the information they determine to be appropriate. CDER might also include its own learnings from the pandemic in indicating the information CDER finds most helpful, and the information that CDER does not immediately need.

- Please consider applying the same flexibility to the reporting timeframes, particularly the one-business-day reporting timeframe. A one-day reporting timeframe is neither possible nor practical when implementing an ever-evolving Plan, or in the subsequent phased return to normal operations. The use of risk assessment principles could help manufacturers prioritize communication of the most critical information to CDER. It also would allow manufacturers to balance ongoing Plan implementation with communication of less-critical information to the Agency.

- Consider the format in which CDER would like to receive this information. Is an email the most efficient means of communicating critical information? Could fillable online forms be linked to a sortable spreadsheet within CDER? Are there circumstances in which a manufacturer should provide information by telephone first, with email follow-up? Emails are time-intensive for manufacturers to write and for Agency staff to review and triage, so we welcome alternative solutions.

- Consider whether any changes to this section are necessary to align with *Notifying FDA of a Permanent Discontinuance or Interruption in Manufacturing Under Section 506C of the FD&C Act: Guidance for Industry*. Since the emails described in section III.F "are intended to help CDER maintain awareness of any potential shortage situations and act accordingly to avoid or mitigate them," emails sent to CDERStaffingNotice@fda.hhs.gov under this guidance have a similar, though not identical, purpose as emails sent to DrugShortages@fda.hhs.gov. Is this system providing FDA the information it needs in an actionable manner in the current pandemic? In light of the other pressures on manufacturers and their employees in a crisis situation, can CDER simplify any of these steps without losing access to information the Agency needs?

Second, while this guidance appropriately focuses on production of MNPs, we suggest that FDA further discuss in sections II and III the impacts on the manufacture of products that are not currently considered "medically necessary." In prioritizing products that are

medically necessary, what consideration should be given to other products? What changes might be acceptable in their manufacture? These other products might be more robust, with more historical manufacturing data. Applying mitigation strategies to those products might free capacity for the manufacture of MNPs, while minimizing the risk to quality. Further, as we have seen in the current pandemic, products may become medically necessary as treatment data evolves or as alternative treatments enter shortage.

Third, for clarity, PDA asks that CDER add the following examples to the list that begins at the bottom of page 5 of activities that may be reduced provided that the change will not unacceptably reduce assurance of product quality. We believe that these examples reflect FDA's intent:

- Release batches conditionally without full testing being completed for attributes that are at very low risk based on the executed risk assessments and stability data.
- Allowing extension of the timeline for investigation of complaints resulting from shipment delays on returned samples.

Fourth, because the tips in section IV, *Optimization and Demonstration of Preparedness,* are useful, PDA recommends that FDA move that text to the FDA website. If it were on the website rather than in a guidance, that information may be more widely accessible, could be referenced by other FDA Centers, and could be more easily revised for application to a variety of different scenarios.

Fifth, in section III.A on page 3, CDER mentions that firms may have "plans in place to maintain business continuity in an emergency." Because the guidance otherwise refers to "emergency plans," it is not clear whether CDER is trying to distinguish emergency plans from business continuity plans. If CDER is merely trying to indicate that the emergency plans discussed in this guidance may take different forms and have different names, consider revising this sentence to state that explicitly, e.g., "Firms may already have Plans in place, which might operate under a different name, such as 'business continuity plan.'"

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

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

Sincerely,
Richard Johnson
President and CEO, PDA
cc: Glenn Wright, PDA; Ruth Miller, PDA

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New Vial Tech Shows Promise for Pharma Productivity

Dawn Watson and Jeff Cremi, Merck & Co., Inc.

Advances in pharmaceutical glass packaging offer advantages for both patients and manufacturers, but the potential of new innovations will not be reached without rigorous testing and line trials to confirm their benefits.

Valor® Glass, one example of such new technology, was introduced in 2017 as a tubular glass packaging solution with Type I hydrolytic performance that would substantially reduce particle contamination and prevent cracks. The idea was that its use would significantly increase throughput for pharmaceutical manufacturers ***(1–3).*** Considering that the U.S. FDA has called for improvement in glass manufacturing ***(4),*** Merck & Co. conducted a series of line trials to ensure the compatibility of Valor Glass vials with existing and new lines. The goal was to demonstrate that this innovative product could be introduced as a "drop in" solution and, potentially, deliver a higher quality glass solution. So, the company compared the performance of Valor Glass vials against the conventional borosilicate (Type I) vials currently used on their manufacturing lines.

To start the trials, a cross-functional team was established to provide the necessary expertise and experience to enable an objective assessment of the new technology. Strong sponsorship of the team ensured the availability of appropriate resources, funding and line time. This team developed a standard assessment approach that would be applied across multiple sites and products, so data gathered across various lines could be easily compared. Trials were designed to assess machinability performance, particulate generation, interventions, glass breakage and performance using visual inspection on filling and packaging lines.

The team, which included experts in glass manufacturing and handling, product

impact/stability, manufacturing process, quality risk management and regulatory affairs, evaluated the performance of the vials. They set success criteria and maintained an objective viewpoint throughout the various line trials. Early engagement with regulatory agencies facilitated understanding of expectations and requirements needed for implementation ***(5).***

Study Protocol Overview and Summary Results

For initial assessment, multiple engineering trials were run on a single line, demonstrating that the Valor Glass vials performed better when compared to historic conventional glass data. The new vials enabled a higher effective line speed (more vials filled and passing final inspection per unit of time), required fewer glass-related interventions and generated lower particulate contamination. These line trials tested 50,000 to more than 1,000,000 Valor vials These line trials ranged from 50,000 to more than1,000,000 Valor vials. The result of the largest line trial is summarized in **Table 1.**

Table 1 Results of an Engineering Line Trial Comparing Valor Glass to Conventional Glass

Machinability Outcome			
	Conventional Glass	Valor® Glass	Performance of Valor Glass Vials compared to Conventional Vials
Effective Line Speed	326 +/- 26 vpm	440 vpm	25% improvement
Interventions	247	95	61% reduction
Particulates (at In-feed)	50	4	92% reduction in nonviable particles at in-feed locations
Lubrication Events	5	0	100%

The results of the line trial confirmed the improved performance of Valor Glass vials compared to the conventional borosilicate vials currently in use.

Additional trials were conducted on different filling lines, including relatively new filling lines. The trials varied from hours to a single day of run time, with volumes ranging from 5,000 to 150,000 vials. Machinability was successful on each of these lines.

Efficiency on the Line

Valor Glass vials have a coating applied only to the outside of the vial, so there is no increased risk with respect to extractables and leachables. The external coating reduces the coefficient of friction of the vials, allowing them to process with less resistance on a filling line than conventional borosilicate vials. Consequently, the improved flow required adjustments to certain filling lines—lines where vials ➤

are moved "en masse" with accumulation points or that move glass via backpressure—to accommodate the smoother transfer of vials and the new flow pattern **(Figure 1)**.

As shown in the observation of Lubrication Events in **Table 1,** the external coating on the vials eliminated the need for the application of lubricant on the line, which is used during the filling process for conventional borosilicate glass vials to improve glass flow and reduce glass events.

Crack Prevention

Valor Glass is inherently stronger and more damage-resistant than borosilicate vials. The product was designed with significantly greater mechanical strength and higher internal energy than conventional borosilicate glass vials, which also prevents the occurrence of cracks. While Valor Glass is inherently stronger, breakage is still possible. Unlike conventional vials that can incur difficult-to-detect cracks when severely damaged, Valor Glass is engineered to break rather than crack when severely damaged, and it breaks in a more controlled manner than conventional vials. That breakage signals a quality issue, such as improper line set-up, allowing operators to take corrective action immediately. Breakage events with Valor Glass vials, for example, can enable line operators to detect and correct such issues as:

- Misaligned transition that impacts the heel of the vial
- Improper capper set-up that causes the disk/rail to damage the neck of the vial
- Filling-needle strikes that occur at the top of the vial
- The Valor Glass has not damaged equipment or exhibited cracks in any of the line testing performed to date.

Lyophilization with Valor Glass

The team also compared lyophilization between Valor Glass and current vials, following a multistage approach. The team established equivalence for critical dimensions between Valor Glass vials and conventional borosilicate vials. Laboratory-scale runs were conducted to assess respective freezing kinetics of both types of vials. Head-to-head comparisons were conducted using gravimetric analysis,

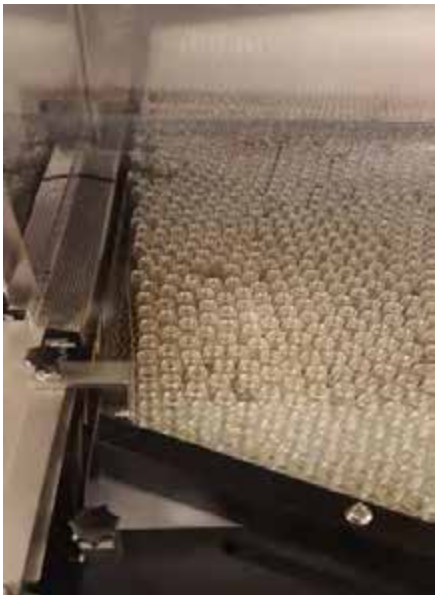

Figure 1 "En Masse" Movement of Glass on One of the First Trial Lines

Figure 2 Overall Appearance of Lyophilization Cakes in the Commercial-Scale Run

and sublimation rate data were used to determine the relative heat transfer coefficients via mathematical modeling. The studies showed that Valor Glass had a slightly lower average heat transfer coefficient relative to conventional borosilicate glass. This finding was negligible, however, with no anticipated impact to the current primary drying times for the production lyophilization cycle.

Following these comparability tests, commercial runs were conducted to assess the freezing profile, product moisture content, chamber pressure and overall lyophilization cake appearance (**Figure 2**). The results of the commercial-scale testing are summarized in **Table 2.**

Both laboratory- and commercial-scale testing demonstrated there was no need for adjustment in lyophilization-cycle parameters. No Valor Glass vials broke or cracked through the lyophilization process. The lyophilization performance of Valor Glass was deemed equivalent to that of conventional borosilicate glass vials for this specific application.

Thoughts on Control Strategy

As with most packaging changes, the engineering trials required minor equipment adjustments to enable smoother operations. The external coating of the Valor Glass vials imparts a significantly lower coefficient of friction than conventional glass, which can impact vial handling. This should be considered for machinability. The coating is durable but can be affected by extended durations at depyrogenation temperatures. The time should be monitored during extended line stoppages within the depyrogenation tunnel, and control measures should be set up to reduce the overall temperature exposure during prolonged stoppages to prevent

Table 2 Comparability Assessment of Valor Glass versus Conventional Borosilicate Vials for Lyophilization

Lyophilization Comparability	Commercial-Scale Results
Freezing Profile and Chamber Pressure	Comparable
Moisture Mapping	Moisture results were within specification and comparable to historical performance
Lyophilization Cake Appearance	No change was observed

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> The vials were either intact or broken

coating degradation. Coating degradation results in a slight increase in coefficient of friction, but no loss in functional performance over the typical duration for normal processing at depyrogenation temperatures.

Valor Glass has an engineered binary response to damage, meaning that the vial is intact, or it breaks under extreme insult. This property could potentially enable enhanced quality assurance. When damaged in the uncoated flange region (specifically, the radii), Valor Glass may chip comparably to borosilicate containers; however, flange damage will not result in cracks. Breakage events with Valor Glass serve as a clear signal that suboptimal conditions may be present. While no equipment was damaged in any of the trials, precision in set-up and sensitivity to dimensional variation must be factored into engineering trials. The increased strength of the Valor Glass vial may also require equipment adjustments to ensure appropriate over-torque settings are in place in case of an event.

Any potential dimensional differences of the test vials compared to the current conventional borosilicate vials in use must also be evaluated and assessed. This is important to confirm both machinability and lyophilization equivalence.

Discussion

Valor Glass vials were specifically designed for use by pharmaceutical manufacturers. This new package solution is optimized to resist breakage and prevent cracks through ion exchange strengthening and a thermally stable exterior coating.

The external coating of Valor Glass imparts a low coefficient of friction, which should be considered for machinability. It also protects vials from damage or insults that can occur during processing, resulting in fewer particulates. The results of line trials for Valor Glass vials demonstrated more effective line speeds, fewer glass-related interventions required on the line and a significant reduction in particulate levels.

In addition, the Valor Glass vials showed no evidence of cracks in any of the trials. Instead, they exhibited a binary behavior in coated regions of the vial. The vials were either intact or broken; but cracks did not form in response to damage events. During machinability of Valor Glass vials, finish chips were noted, but only during atypical handling or when needle strikes resulted from misalignment. Valor Glass crack prevention is an important finding considering the challenges associated with cracked containers. These results may indicate an opportunity to decouple break events from concerns related to loss of sterility or purity of batch and could, ultimately, lead to a reevaluation of current regulatory notification expectations related to broken containers.

Conclusion

These trials demonstrated that Valor Glass has the potential to reduce particulate contamination, prevent cracks, and enhance throughput. Enabling the benefits of Valor Glass may require some optimization of manufacturing control strategies related to extended time in depyrogenation chambers and equipment setup, as discussed above. In addition, the unique attribute relating to crack prevention has the potential to reduce response activities related to broken containers.

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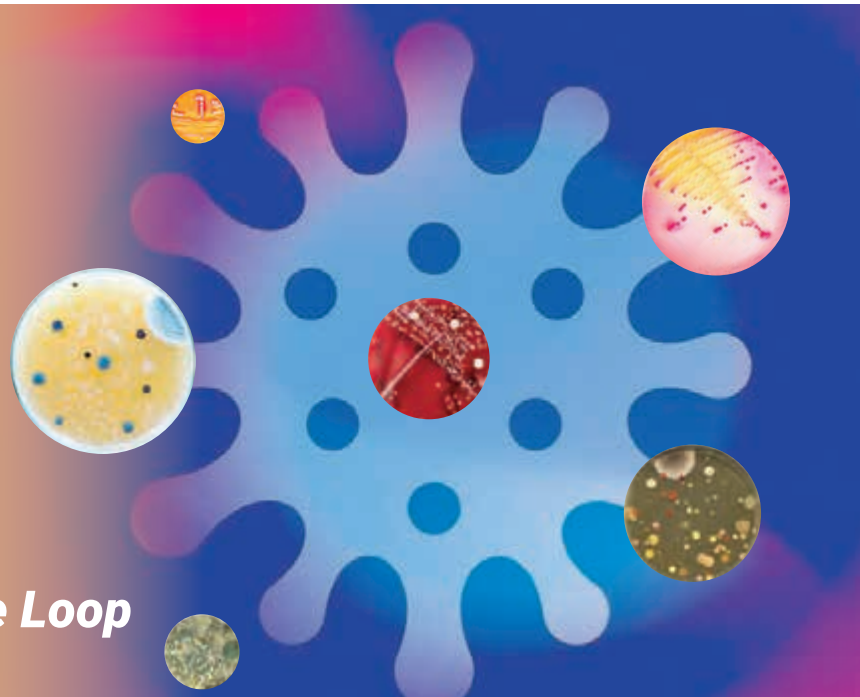

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Real-World Applications of Rapid Micro Methods

Tony Cundell, PhD, Microbiological Consulting

Though rapid microbial methods present the opportunity to conduct efficient testing across pharma, most manufacturers, whether due to method application or regulatory/compendial uncertainties, have yet to adopt them.

The *2019 PDA Rapid Microbiological Methods Workshop,* held in Rockville, Md., following the *14th Annual PDA Global Conference on Pharmaceutical Microbiology* provided an opportunity for members of the industry to hear from global regulators and compendial representatives on the topic. The 130 participants, 11 attending virtually via a live stream over the Web, learned from case studies how some firms have successfully implemented rapid methods.

The workshop opened with a comprehensive discussion of U.S. FDA regulatory expectations from **Erika Pfeiler**, PhD, Supervisory Microbiologist, CDER, and **Simleen Kaur**, Biologist, CBER. Former MHRA Inspector **Andrew Hopkins** offered an EU perspective**.** A highlight of the session was a presentation by **Haijing Hu,** PhD, Senior Microbiologist, CDER, on the application of rapid microbial methods in sterile compounding.

The afternoon concluded with talks exploring chapters on rapid microbiological methods in the U.S., European and Japanese pharmacopeias. The organizers were fortunate to welcome **Yutaka Kikuchi**, PhD, Professor, Chiba Prefectural University of Health Science, who shared his experience with Japanese practices on rapid microbial method in the pharmaceutical sciences. **Tony Cundell,** PhD, Principal Consultant, Microbiological Consulting, and a member of the 2015–2020 USP Microbiology Committee of Experts, spoke from USP's point of view while **Sven M. Deutschmann,** PhD, Head of Global Analytical Science & Technology, Roche Diagnostics, provided information on Ph. Eur. Chapter 5.1.6 "Alternative Methods for Control of Microbiological Quality." Collectively, these talks underscored the varying levels of acceptance for rapid methods by global pharmacopeias provided certain conditions are met.

Day 2 of the workshop featured a number of case studies on rapid microbial methods, including real-world applications. **Frederic Ayers,** Research Scientist, Eli Lilly, looked at real-time feedback to control for biofluorescent particles. **Andrew Finnerty,** General Manager, Centre for Cell Manufacturing Ireland (CCMI) at NUI Galway, showed how to use rapid sterility testing on advanced therapy medicinal products. Here, a product is often injected directly into a single patient within a short time frame where traditional sterility tests are inadequate. Similarly, compounded pharmaceutical products can also be produced as individual batches. **Anthony Grilli,** MS, Owner, FOCUS Laboratories/Atlas Analytical, presented a case study on using a real-time rapid microbial detection solution for releasing a compounded product.

Other case studies addressed rapid mycoplasma testing, real-time PCR detection of *Burkholderia cepacia* and automated colony-counting.

The workshop closed with an "Ask the Experts and Regulators" panel that provoked a lively exchange between the audience and panel members **James Kenney** (FDA, CBER), **Michael Miller,** PhD, President Microbiology Consultants, Erika Pfeiler, Tony Cundell, Sven Deutschmann and Andrew Hopkins. The topics of discussion ranged from satisfying global regulatory requirements to parametric release to the impact of Brexit on testing requirements.

The presentations at the *2019 PDA Rapid Microbiological Methods Workshop* were comprehensive, compelling and insightful. PDA will host a second workshop, the *2020 PDA Rapid Microbiological Methods Workshop,* in October. The upcoming workshop will likely feature more in-depth discussion on rapid methods as the industry moves toward acceptance of these innovative methods.

Closed System Transfer Devices Prove Hot PDA Topic

Bettine Boltres, PhD, West Pharmaceutical Services, Inc.

In PDA's continuing effort to present topics of interest to the pharmaceutical industry, this year's Parenteral Packaging Conference featured two sessions on closed system transfer devices (CSTDs). Due to gaps in the information about CSTDs, this is a critical subject, as the overwhelming number of abstracts we received attests. Consequently, the planning committee dedicated two sessions to CSTDs featuring presentations by the following experts:

- **Cathy Zhao,** West Pharmaceutical Services, "Development of Guidance for the Interconnectibility between Vial Container Closure Systems and Vial Transfer Devices" **[Author's Note:** Zhao's article on closed system transfer devices can be read at the *PDA Letter* website**.]**
- **Kunjal Oza,** Genentech/Roche, "Considerations for Using Closed System Transfer Devices with Biological Drug Products"
- **Katharina Golly,** Novartis, "CSTDs: How to Apply USP in Combination Product Development"
- **Holger Roehl,** F. Hoffmann-La Roche, "CSTD Selection for an Established Container Closure System - A Case Study"

From the presentations and subsequent Q&A, it was clear that many pharmaceutical companies are struggling with similar issues resulting primarily from a lack of standardization among CSTDs available on the market. A visual comparison makes this obvious — no standard shape or dimensions, not even a standard construction material for the fluid path. CSTDs can be made of polypropylene, polytetrafluoroethylene, stainless steel, acrylonitrile butadiene styrene, polyvinyl chloride, polycarbonate, silicone, thermoplastic elastomers, or polyisoprene, to name a few. The variety of parameters for these devices necessitates they be handled differently, not to mention the diverse selection of the requisite counterparts — stoppers and vials.

Hospital contracts with specific device suppliers and administrative procedures often locks institutions into using a specific manufacturer's device, even if the device does not properly fit a wide variety of drug container closure systems. This

Another issue that raised much discussion among participants is chemical compatibility with the device

can create drug product handling issues, like broken vials due to the excessive forces that may be applied to pierce the CSTD spike through a stopper. High puncture forces may also push the stopper into the vial, as presented at the *2018 PDA Parenteral Packaging Conference*. These container closure failures represent obvious challenges. Less obvious, but of equal concern, is a topic addressed repeatedly in PDA presentations — the significant number of both subvisible and visible particles generated during CSTD use. Most particles found were silicone, but some resulted from the manufacturing material of the device, the rubber stopper or even aggregated proteins. Studies also confirmed how differently these diverse CSTDs performed; while some had a very low count, others generated thousands of particles.

One concern raised by the PDA audience was CSTDs being used to **extend the use of vials that do not contain antimicrobial preservatives for medicines**. Not only is this off-label use of CSTDs not qualified for this procedure, but it raises the potential of creating a dangerous situation should a breach in sterility not be detected before the drug is administered to a patient. To be fair to CTSDs, they were initially intended to protect the user from the hazardous drug inside the vial. They were not designed to maintain sterility without preservatives, nor were they historically tested for chemical compatibility or particle generation.

As the development of biological drugs evolve, use of these sophisticated molecules carries a high price. Drug companies do not want to lose the molecules through interactions with a device. As reported by all conference presenters, the impact of drug holdup volume is of particular concern, as it can result in drug loss and improper dosing.

Another issue that raised much discussion among participants is chemical compatibility with the device. According to USP General Chapter <800>, CSTDs should only be used if they are compatible with the drug. Yet a Genentech-sponsored survey found that only 50% of hospitals reach out to device manufacturers for compatibility data.

That, in turn, leaves behind many unanswered questions: How is compatibility defined? What are measurable criteria? And, how are extractables and leachables accounted for? The survey showed that hospitals in every country, and some within individual countries, are dealing with this challenge differently. The U.S. National Institute of Occupational Safety and Health (NIOSH) publishes a list of hazardous drugs; however, the Genentech survey showed that not all hospitals or all countries, use it. In fact, some hospitals create their own lists.

Clearly, common global standards and guidances for CSTDs are needed but lacking.

Concerning standardization, participants agreed that the Product Quality Research Institute (PQRI) project, in which PDA is also involved, is a first step in the right direction. The broad scope of the project covers vial transfer systems, in general, and the interconnectability of vial container closure systems and vial transfer devices, specifically. Many key stakeholders are working together on developing and promoting best practices and a guidance for CSTDs, including relevant quality and performance requirements, that can be used by industry.

Some pharmaceutical companies already include CSTDs in their product development. This provides greater confidence in a successful preparation and treatment. But with that comes additional responsibility for the pharmaceutical company in the form of a greater regulatory burden, as drug and device require co-packaging and a more stringent regulatory process. This scenario, though, often causes frustration for pharmaceutical companies when they see some hospitals discarding the co-packaged device and using their own, instead, one that might be less suited in a specific case.

This last point instigated a very lively discussion that resolved in agreement — the flow of information and education must be increased significantly. Hospital personnel would benefit from more in-person, on-site training to facilitate an understanding of the implications and consequences of improper CSTD usage. On the other hand, handling of CSTDs needs to be facilitated to support caregivers in their time-critical occupation.

By the end of the two sessions, one thing was very clear: CSTDs is a hot topic that warrants a follow-up session at next year's PDA *Parenteral Packaging Conference.* Join this important discussion at the 2021 conference next March and help shape the future of parenteral packaging.

About the Author

As Principal of Scientific Affairs, **Bettine Boltres,** PhD, who moderated the two CSTD conference sessions, supports the scientific exchange between West and the pharmaceutical industry.

Tamer Helmy

Director, Quality Control | ***Molecular Templates*** | Member Since 2017 | Mansfield, TX

My ultimate goal is to help patients receive a safe quality product

Why did you join PDA?
When I had the role of a principal scientist of quality, I was responsible for method development and validation. I first heard about PDA when I had method validation questions, and while searching for answers, I was referred to PDA technical reports. I was impressed with the knowledge and guidance to the industry that is provided by PDA.

What is your favorite part of serving on the *PDA Letter* Editorial Committee?
The best part is the wide range of topics submitted for publication which allows for continuous exposure to different aspects of the pharmaceutical industry. Meanwhile, you get to be involved in shaping the *PDA Letter.*

Do you have any advice for new volunteers?
PDA is a great organization that connects pharmaceutical industry professionals globally and provides technical expertise in several areas. I would advise new volunteers to get involved and participate as much as they can in PDA activities so they can take advantage of the benefits PDA has to offer.

What significant changes have occurred in your area of expertise?
Robotics and single-use systems have grown in recent years. Advanced aseptic technologies have evolved to address the need for less human interventions. Humans are the main source of contamination in cleanrooms; therefore, the less human interventions, the lower the risk of contamination.

What inspired you to choose your current career path?
Improving human life. My ultimate goal is to help patients receive a safe quality product while maintaining my appetite for finding solutions and improving processes.

Do you have a hobby?
Appreciation of art. When I find time, I enjoy model railroad building. I always liked trains, and when I lived in North Carolina, I attended a model railroad convention where I met a group of train enthusiasts who invited me to join their club. I was fascinated with the artistic details of the railroad layouts and I decided to start building mine. When building a railroad layout, you design the town, buildings, rails, electrical connections and even the landscaping.

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Critical Resources for the Industry

It goes without saying that the COVID-19 epidemic has upended our industry. Shortages of critical medicines loom and there is also shortage of disinfectants and sanitizers along with personal protective equipment (PPE), e.g., masks and gowns. Of course, PPE is also needed to meet our GMP standards and associated Standard Operating Procedures (SOP).

As chair of PDA's new temporary COVID-19 task force, I am excited about this opportunity to help the pharma and biotech industries as they face the twin challenges of developing and manufacturing treatments and potential vaccines for the novel coronavirus while also working hard to ensure a stable supply of the sterile products used to treat other conditions. Naturally, social distancing requirements, absences and the need for enhancing cleaning and disinfection are some of the issues facing us.

Task force members, **Anthony Cundell, Dennis Guilfoyle, Thomas Kreil** and myself submitted a paper "Controls to Minimize Disruption of the Pharmaceutical Supply Chain During the Covid-19 Pandemic," for publication in the *PDA JPST*. It is currently available as an accepted article (https://journal.pda.org/content/early/2020/05/28/pdajpst.2020.012021). This paper provides background information on the virus and its history, examines spread and controls in the context of GMP, analyzes the current state of the industry as far as preparedness and makes recommendations.

We also hosted a webinar on May 27 featuring three members of the task force, Thomas Kreil, Anthony Cundell and **James Polarine**. They touched on the makeup of the virus, supply chain challenges and cleaning and disinfection strategies. The task force also plans further webinars, so continue to check out the PDA events page.

The task force is also planning to draft a technical report and/or other best practice documents for industry.

This is a challenging time for the industry. At the same time, we can learn from it to prepare for other potential disruptive events. PDA will continue to support its members in the industry by providing comprehensive resources to ensure the stable supply of medicines.

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PDA is committed to maintaining opportunities for volunteers and individuals from the pharmaceutical industry to meet, wherever we can do so. PDA considers safety and health of event attendees as a subject of utmost importance. PDA has implemented a set of measures to protect participants and staff from potential risks related to COVID-19 as best as possible. This includes a close and regular monitoring of the situation, adherence to recommendations of health authorities and official travel warnings, precautions being implemented at our venues, and the possibility of remote presentations or virtual events.

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