People • Science • Regulation

PDA Letter

Volume LVI • Issue 4 www.pda.org/pdaletter July/August 2020

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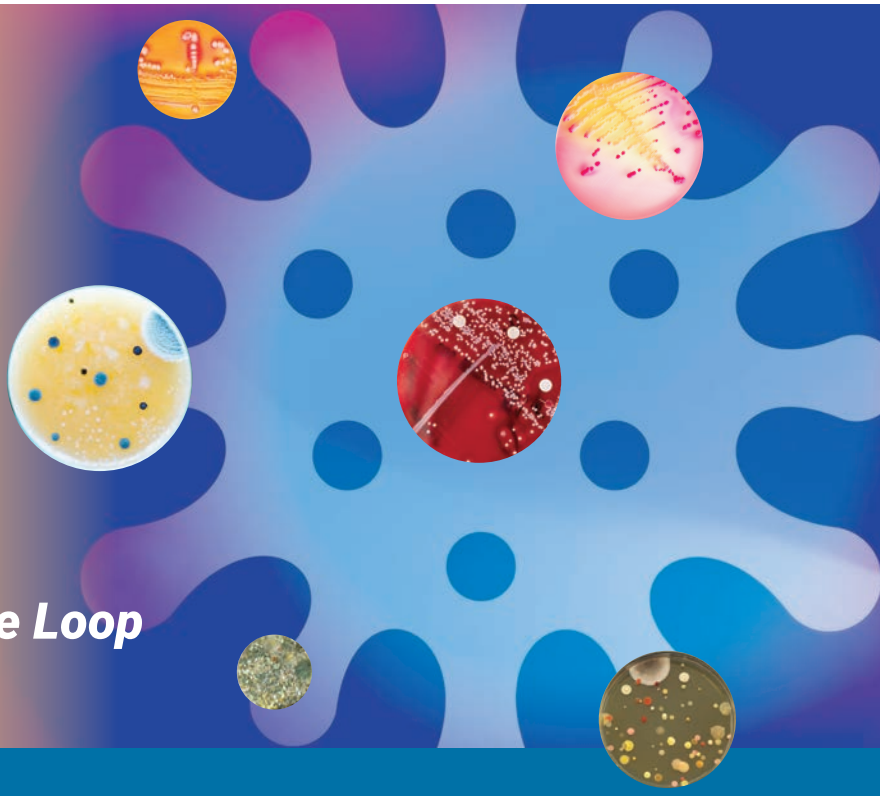
PDA
Parenteral Drug Association

pda.org/2020micro

15th Annual PDA Global Conference on Pharmaceutical Microbiology

Keeping Microbiology in the Loop



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

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OCTOBER 19-21

VIRTUAL EXHIBITION: OCT. 19-20

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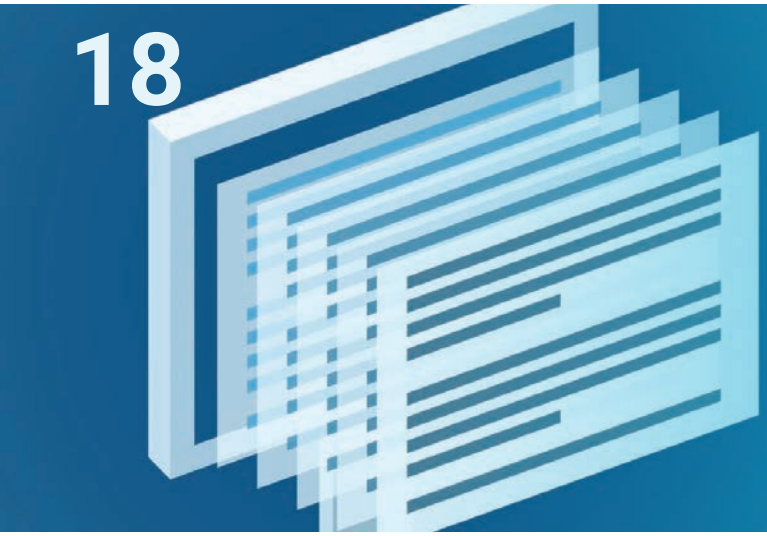
July/August 2020 PDA Letter

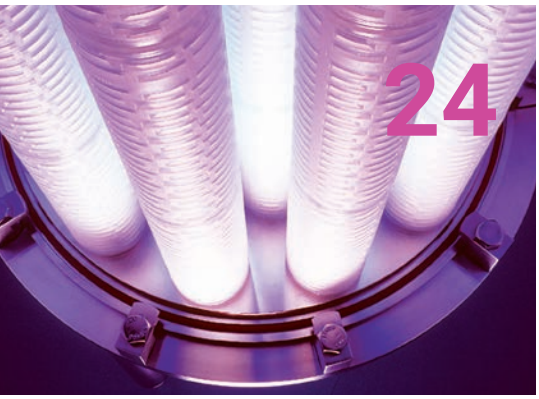


Regulator Develops Remote Inspection Process Due to Pandemic

Vladislav Shestakov, Russian State Institute of Drugs and Good Practices, and Elizabeth Meyers, Amgen

Russia's State Institute of Drugs and Good Practices (SID&GP) recently conducted its first remote GMP inspection of a manufacturing facility for an international pharmaceutical company. The "social distancing" restrictions in place due to Covid-19 limit the number of staff on site, necessitating the novel alternative. This article presents both sides of the experience to provide guidance for both manufacturers and regulators around the globe as they migrate to this new form of inspection.

Cover Art Illustrated by Katja Yount



The Use of Scientific Data to Assess and Control Risks Associated with Sterilizing Filtration

William Peterson, Merck & Co.

In recent years, a desire to minimize the risks associated with sterilizing filtration has prompted much discussion on the need for pre-use/post-sterilization integrity testing (PUP-SIT) to detect nonintegral filters *before they are used* if there is any risk of not detecting them after the filtration process. The purpose of this article is to present guidance to industry (sterile drug manufacturers, filter suppliers and regulators) on how to develop and evaluate scientific data to prevent undetected nonintegral sterilizing filters.

Industry Must Move Away from Dye Ingress Test

Oliver Stauffer, PTI

Few events have contributed more to society's understanding of pharmaceutical container closure integrity than the 1970 outbreak of bacterial infections from IV fluid container failure. Eight hospitals across seven states received compromised IV fluids, leading to nine deaths. The outbreak was eventually attributed to closure failure of IV fluid bottles during the sterilization process. The closure system failure was not something that would be detected with CCI protocols of that time.

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

Subscriptions are not available.

Departments

New at the PDA Letter Online

> **PDA Podcasts** | July/August *PDA Letter*
> The July/August *PDA Letter* podcast is now available! Hear GSK's Michele Myers discuss advanced therapeutic products at the 2016 PDA Annual Meeting.

> Pharma Firm Explores RFID for Prefilled Syringes
> Traceability can be a complex subject due the different process requirements and company needs.

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A Fond Farewell to Readers

Rebecca Stauffer

I have had the honor to work on the *PDA Letter* since 2012 and to lead the publication as Managing Editor beginning in 2017.

It has been an honor to lead the *PDA Letter* through a number of major changes. In 2015, we expanded the online version of the Letter to include all print content to great fanfare. Previously, only the PDF and three select articles were published online.

That same year, I had the chance to become a scriptwriter, gaffer, location scout and even wardrobe consultant for the first in our "On the Issue" videos. Over time, our filming equipment has evolved from clamp lights purchased at a local hardware store to professional lighting equipment.

In addition to travelling to PDA's U.S. conferences, it has been a pleasure travelling to cover conferences hosted by the PDA Europe staff. This included meetings in Munich, London and Vienna.

Earlier this year saw another major change, the reduction of our print content from ten issues to six and switch of the publishing focus to online content. In hindsight, this turned out to be a prescient decision.

Since March, I have witnessed the PDA community come together to support each other in the face of a grave pandemic. Recognizing that information is critical for the pharma industry right now, all new Letter content has been open access since the end of March. We continue to publish content supporting PDA members switching to work from home, dealing with remote inspections and facing greater manufacturing challenges such as higher absentee rates and social distancing.

We also just launched our second regional edition of the *PDA Letter,* aimed at audiences in Asia-Pacific countries. This follows the successful launch of the European regional edition in April. I am proud to have been part of expanding the global reach of the *PDA Letter.*

I am sad to leave my PDA family. I know the publication will be in good hands. **Walter Morris,** PDA's Senior Director of Publishing and Press Relations, will resume his former role as Managing Editor in the interim.

These have been trying times of late and I am proud to have witnessed the industry come together to produce COVID-19 treatments on short notice and seek a potential vaccine. PDA has expanded its Web offerings to include webinars and online education courses; I consider the *PDA Letter* another great tool.

I will miss everyone and am proud to leave the Letter on a high note.

Walter Morris, Senior Director of Publishing

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Volunteers Needed: Event Reports and Other Articles

Times are hard for everyone across the globe with the pandemic disrupting lives, businesses, education, and medical systems. Those in the PDA community are busier than ever to meet the challenges while many adjust to work-from-home or disrupted on-site work arrangements. PDA is no different. We are working very hard to move our industry-leading events from on-site to virtual, while at the same time managing a sudden and significant decline in revenue. But the mission of *Connecting People, Science and Regulation*® has never been more critical.

Throughout the pandemic, our members have continued submitting articles! The article pipeline, however, is slowing. Combine this with the departure of Managing Editor **Rebecca Stauffer,** we will experience significant gaps in our coverage of PDA's online events.

PDA is looking to our members to fill that gap. Just a few weeks ago, the virtual **PDA Annual Meeting** concluded. If you attended that terrific online event (sessions are still available to view), you can share your experience with the entire PDA community with a short (500-1000 words) report on sessions you attended.

Those attending the upcoming **virtual PDA/FDA Joint Regulatory Conference** can help by sending short reports to the *PDA Letter.* Of course, following that signature event, PDA will host (online) the Pharmaceutical Microbiology and Prefilled Syringes events. Volunteer reporters for all these meetings are needed.

Putting on your best Clark Kent face is not the only way to contribute to the Letter. Each month, we publish two feature-length articles (1500-2000 words) on strategic PDA topics:

- Aseptic Processing/Sterile Products Manufacture
- Biopharmaceuticals & Biotechnology
- Manufacturing Science
- Quality & Regulatory
- Supply Chain & Outsourcing

Also, we publish shorter articles (500-1000 words) on new technologies, methods and hot regulatory trends (warning letter evaluations, GMP advice, new guidances, etc.).

Just a word on important distinctions between the *PDA Letter* and the *PDA Journal of Pharmaceutical Science and Technology (JPST).* Any manuscript that is data- and reference-heavy and/or is more than 2000 words belongs in the JPST. In 2019, a new, thorough submission guide was posted on the JPST website (https://journal.pda.org/content/author-resourcessubmit-paper). All authors to JPST are required to read these guidelines in advance and follow them, because JPST is not a full-service magazine. Authors to JPST are responsible for ensuring that their manuscripts are edited and follow the norms of U.S. English grammar and syntax. Resources for editing services are noted in the author guide. In addition, all submissions to JPST will undergo peer review.

Letter articles should be shorter (under 2000 words) and should never present new scientific data. There is no peer-review in the Letter process, and the Letter will not allow publication of unverified (peer-reviewed) data. In addition, Letter articles should have short, quick "ledes" and avoid lengthy introductions and background information.

I look forward to an influx of member articles in the second half of 2020. I wish everyone the best as we all work together to get through these trying times.

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U.S. FDA's Douglas Throckmorton to Open *PDA/FDA Joint Regulatory Conference*

Douglas Throckmorton, MD, Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research (CDER), U.S. FDA, has been confirmed as an opening plenary speaker of the 2020 PDA/FDA Joint Regulatory Conference, which will be held virtually Sept. 14 – 16.

The theme of the 2020 conference is "The Future Is Now: Effective Quality Management and Robust Manufacturing." Speakers from the U.S. FDA, other regulatory bodies, and industry will explore the continuing evolution of innovative manufacturing capabilities and the potential effect on quality, compliance, and regulatory lifecycle paradigms.

FDA senior officials will discuss Center-specific initiatives as well as provide compliance updates in what has become one of the most popular recurring sessions of the event.

PDA and the U.S. FDA once again are cosponsoring the PDA/FDA Joint Regulatory Conference, which is now in its 29th year. Because of the ongoing challenges of the COVID-19 pandemic, the U.S. FDA and PDA agreed to hold the event virtually.

This flagship conference consistently provides a unique opportunity to hear from and engage with numerous regulatory and industry leaders concerning the latest manufacturing, quality, supply, and related compliance issues in an ever-evolving landscape.

Tia Bush, Senior Vice President, Quality, *Amgen, Inc.,* is a confirmed speaker for the closing plenary session. PDA had confirmed other industry expert speakers from GlaxoSmithKline PLC, AstraZeneca PLC, Merck Sharpe & Dohme Corp., Eli Lilly and Company, and Sanofi Pasteur.

Among the many topics these and other industry and regulatory authority experts will address are:

- Commercialization challenges in cell and gene therapy
- Data analytics in manufacturing
- De-risking your supply chain
- Quality assurance role in 2020 and beyond
- OOS investigations
- U.S. FDA Emerging Technology program

Continued at bottom of page 11

BSR/PDA Standard 02-201x Cryopreservation Standard Available for Public Comment

BSR/PDA Standard 02-201x, Cryopreservation of Cells for Use in Cell Therapies and Regenerative Medicine Manufacturing is now available for public comment. To receive a copy of this draft standard, email PDA at standards@pda.org. The public comments period concludes September 7, 2020 EDT. There is no charge for the draft standard.

To better harmonize cryopreservation of advanced therapies, including cell and gene therapies, PDA convened a working group comprising experts from academia, industry, and governmental regulatory bodies to compile and draft current best practices into a single reference document. This standard will assist both commercial and clinical groups with their cryopreservation efforts.

On August 7, 2020 BSR/PDA Standard 04-201x, Phage Retention Nomenclature Rating for Small and Large Virus Retentive Filters will also be released for public comment.

For more information about PDA's role in standards development, visit: https://www.pda.org/scientific-and-regulatory-affairs/pda-ansi.

Find answers to standard development questions: https://www.pda.org/scientific-and-regulatory-affairs/pda-standards-frequently-asked-questions or reach out to standards@pda.org.

U.S. FDA's Douglas Throckmorton to Open PDA/FDA Joint Regulatory Conference continued from page 10

For more information, visit the 2020 PDA/FDA Joint Regulatory Conference website: https://www.pda.org/global-event-calendar/event-detail/2020-pda-fda-joint-regulatory-conference

Members of the press may request a press pass at the following website: https://www.pda.org/about-pda/press-pass-request-form.

Italy Chapter Looks Ahead

Angela Molaschi, Chapter President

PDA's Italy Chapter held its annual meeting in Milan on Feb. 4, right before the COVID-19 emergency in Italy and around the world.

After a presentation on new guidelines on sterilization methods and Annex 1 revision updates, chapter leaders summarized the chapter's 2019 initiatives, events and successes. The chapter held five main events, including a workshop during the Italian pharma exhibition, *Pharmintech.* The events were successful with great participation by attendees and sponsors. Detailed analysis showed that attendees greatly appreciated the organization and technical/scientific value of the events!

Next, chapter leadership discussed chapter membership and highlighted initiatives to increase it. In 2019, the chapter started collaborating with several Italian universities to increase focus on young professional members. This collaboration has also led to the creation of a master's course focused on sterile product manufacturing.

During the final portion of the meeting, chapter members discussed plans and initiatives for 2020. A lot of new ideas were raised, and several potential events were targeted, including a congress on cleaning and sterilization methods, a workshop on blow-fill-seal manufacturing, and a technical training on advanced *Limulus* amebocyte lysate analysis and risk management. Naturally, due to the emergency situation related to COVID-19, most of the events have been delayed to the second half of 2020 and to 2021, in line with PDA guidelines.

In order to support its members and the pharmaceutical community, however, the chapter has planned a series of webinars on the hottest parenteral topics. The first webinar took place April 21 and covered depyrogenation. For future webinars, check out PDA's Global Event Calendar: https://www.pda.org/global-event-calendar.

In addition, the Italy Chapter will continue cooperating with universities and other associations to promote PDA's global initiatives in support of parenteral manufacturing. The chapter looks forward to working together to Connect People, Science and Regulation®!

ITALIAN

Il 4 Febbraio 2020 è stato un giorno importante per il PDA IT chapter! Si è infatti svolto a Milano il nostro annual meeting con la partecipazione del Comitato Esecutivo, del Comitato Direttivo e dei membri della nostra associazione.

Dopo un'interessante presentazione sulle nuove linee guida relative ai metodi di sterilizzazione e un aggiornamento sulla revisione dell' Annex 1, il Comitato Esecutivo ha presentato iniziative, eventi e successi del 2019.

Cinque eventi sono stati organizzati nell'anno appena trascorso inclusi training tecnici, conferenze, congressi e un workshop presso Pharmintech (Bologna), una delle più importanti e visitate fiere italiane in ambito farmaceutico. Gli eventi hanno avuto un grande successo con attiva ed entusiasta partecipazione di partecipanti e sponsors! Gli eventi del 2019 sono stati analizzati e discussi nel dettaglio con un focus particolare sui feedbacks ricevuti dai partecipanti al termine degli eventi stessi e sulle aree di miglioramento: con nostra grande soddisfazione l'analisi fatta ha mostrato un notevole apprezzamento sia dell'organizzazione sia del valore tecnico e scientifico degli eventi organizzati!

Una sezione della riunione è stata poi dedicata all'analisi della situazione iscritti che si è evidenziata essere stabile ormai da alcuni anni, evidenziando la necessità di attuare nuove iniziative di reclutamento che coinvolgano le tante e importanti realtà farmaceutiche presenti in Italia.

Sempre nel 2019 inoltre PDA IT ha iniziato un'importante collaborazione, di cui siamo molto orgogliosi, con le Università Italiane focalizzata sugli

PDA Who's Who

Angela Molaschi, Technical and Quality Operations Manager, NTC Pharma

The chapter started collaborating with several Italian universities to increase focus on young professional members

"Young Professionals", di cui siamo molto orgogliosi, e che porterà all'attivazione di un Master Universitario che sarà avviato presso l'Università Statale di Milano nell' Ottobre 2020 e che sarà focalizzato sullo "Sviluppo e Produzione di farmaci sterili".

A chiusura della revisione delle attività del 2019 è stato infine presentato il bilancio del Chapter che ha avuto anche quest'anno una chiusura in positivo.

La seconda parte del pomeriggio è poi stata dedicata ai piani e alle iniziative previste per il 2020. Numerose nuove idee sono state presentate e discusse! Una serie di eventi erano stati programmati tra cui un congresso su "Cleaning and Sterilization methods" un workshop dedicato a "BFS manufacturing", un training tecnico su "Advanced LAL analysis" ed infine un congresso sul "Risk Management".

Purtroppo a causa della situazione di emergenza internazionale legata al COVID-19 e al fine di garantire sicurezza e salute di tutti i partecipanti il Chapter Italiano, in linea con le linee guida PDA, ha deciso di posticipare gli eventi alla seconda parte del 2020 e al 2021. Al fine tuttavia di supportare i propri membri e la comunità farmaceutica anche in questo periodo difficile il Chapter Italiano ha deciso di programmare da Aprile a fine 2020 una serie di webinars su tematiche di grande interesse in ambito parenterale. Il primo webinar, sulla tematica della depirogenazione, si è svolto con grande successo il 21 Aprile e una serie di webinars sulla revisione dell'Annex 1 partiranno il 30 Aprile! Il programma dettagliato sarà pubblicato a breve.

In aggiunta all'organizzazione di seminari ed eventi ad alto valore tecnico/scientifico il PDA IT chapter continuerà nel 2020 la collaborazione con le Università e con le altre associazioni farmaceutiche, supportando e rispettando la missione di PDA e promuovendo il networking e la collaborazione nel campo della Produzione di Farmaci Parenterali!

Grazie ancora al Comitato Esecutivo, al Comitato Direttivo e a tutti i partecipanti per la grande giornata passata insieme e per tutto il lavoro svolto con passione e dedizione nel 2019!

Non vediamo l'ora di lavorare ancora insieme come sempre…."Connecting People, Science and Regulation®"!

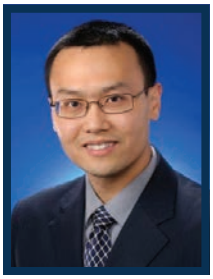
PDA Honor Awards

The winners of the 2019 Honor Award were recognized online and at the PDA Annual Meeting earliers this year. PDA thanks all of the recipients for their contributions to the Association.

PDA Europe Service Appreciation Award

This award honors special efforts that have contributed to the success of PDA's European activities. **Elisabeth Vachette,** Head of Product Management Bags/Mixing/Tanks, Sartorius Stedim Biotech, is recognized for her involvement in the *2019 PDA Europe Pharma Logistics & Outsourced Operations* conference, among other biopharmaceutical and outsourcing-related PDA activities. She supports the biopharmaceutical industry on a worldwide basis, in particular in process design, validation, training and implementation of single-use fluid management technologies.

James P. Agalloco Award



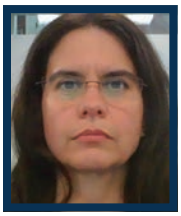
Named in honor of **James Agalloco's** work in developing the PDA Education program, this award recognizes a PDA faculty member who exemplifies outstanding performance in education. PDA grants this recognition to **Lei Li,** PhD, Associate Senior Consultant Engineer, for his work as an instructor for the PDA Education course, "Container Closure Systems and Integrity Testing."

PDA Honor Awards: Distinguished Service Awards

PDA thanks the following individuals for their special contributions to the success of PDA in 2019.

Aaron Goerke, PhD, F. Hoffmann – La Roche AG

Aidan Harrington, PhD, DPS Group Global



Sabrina Restrepo, PhD, Merck & Company Inc.

Lisa Rutter, Partner Therapeutics

Shinji Sugaya, PhD, Towa Pharmaceutical

Frederick D. Simon Award

This award is presented for the best paper published in the *PDA JPST* and is named in honor of the late **Frederick D. Simon,** a former PDA Director of Scientific Affairs. **Philippe Lam,** PhD, Genentech, and **Thomas W. Patapoff,** PhD, received this recognition for their article, "Split-Cakes, Still Delicious," published in the January/February 2019 issue of the *PDA JPST*. Their article explored a potential mechanism for formation of lyophilized pharmaceutical product cakes with unusual internal structures. This article can be found at the JPST website: https://journal.pda.org/content/73/1/16.

PDA Letter Article of the Year

Rajyalakshmi Vathyam received the inaugural *PDA Letter* Article of the Year award for best article published in the *PDA Letter* magazine, per pageview statistics and the opinion of the Editorial Committee. Her article, "Lifecycle Approach Wipes Away Cleaning Validation Concerns," published in the September issue, covered how a multiproduct manufacturer of generic injectable drugs used a lifecycle approach to cleaning validation.

Distinguished Editor/Author Award

This award recognizes the author or editor selected by PDA members for their contribution to PDA's technical books. This year's award went to **Siegfried Schmitt,** PhD, editor of volumes 1 and 2 of *Good Distribution Practice: A Handbook for Healthcare Manufacturers and Suppliers.* These books review GDPs and how to implement them for cost-savings and efficiency. ➤

Service Appreciation Awards

PDA recognizes the following the following individuals for their special contributions to PDA in 2019.

Stephan Krause, PhD, AstraZeneca Biologics

Dipti Gulati, PhD, PJI Biotech

Steven Lynn, Lynn Consulting

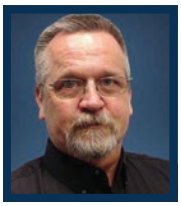
Michael Blackton, Adaptimmune

Melissa Seymour, Biogen

Declan Quinlan, Merck

Vijay Chiruvolu, PhD, Kite Pharma

Ralph Quadflieg, PhD, Laurentius Apotheke



Allen Burgenson, Lonza

Rafik Bishara, PhD

Martin VanTrieste, Civica Rx

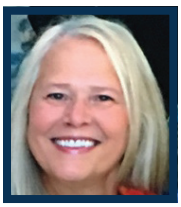
Gary Klaassen, Thermo Fisher Scientific

Erik van Asselt, PhD, MSD

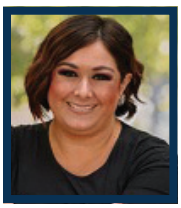
Michael Sadowski, Baxter Healthcare

Ivy Louis, Vienni Training and Consulting LLP

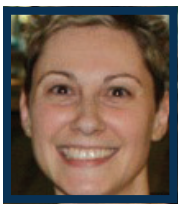
Edward Tidswell, PhD, Merck & Co.



Joyce Bloomfield



Renee Morley



Julie Barlasov-Brown, Merck & Co.

Veronique Davoust, PharmD, Pfizer

Alan Solomon, Baxter

May Huynh

Standard Offers Guide for Supplier Management

Rebecca Stauffer, PDA

Due to increasing concerns about the drug supply chain, global regulators are increasingly looking closely at companies' purchasing control practices. Recognizing this, PDA's first ANSI-approved standard, *ANSI/PDA Standard 001-2020, Enhanced Purchasing Controls to Support the Bio-Pharmaceutical, Pharmaceutical, Medical Devices and Combination Products Industries,* provides a standard purchasing control requirements throughout the product lifecycle.

PDA Chair-Elect, **Susan Schniepp,** and Distinguished Fellow, Regulatory Compliance Associates Inc., and former PDA Chair **Martin VanTrieste,** and President & CEO, Civica Rx, outlined the new standard in a June 24 webinar. Both Schniepp and VanTrieste served on the volunteer committee behind the standard.

[Editor's Note: Martin VanTrieste spoke about the purchasing controls standard at the 2019 PDA/FDA Joint Regulatory Conference in a *PDA Letter On the Issue* video**.]**

Purchasing controls remain more important than ever, according to VanTrieste.

"If we think about it today, many of the recalls are for adulteration," he explained.

In addition to providing a standard for purchasing control requirements, the standard also seeks to ensure that responsibility for compliance is shared at all stages throughout an entire organization. Ultimately, final responsibility falls to the management of the organization. The standard can be used by biopharmaceutical (both proprietary and biosimilars), pharmaceutical (proprietary and generic), medical device and combination product manufacturers.

While the standard expands requirements already defined for FDA-regulated products, manufacturers with products subject to regulations outside the United States may also benefit from the standard.

For one, the standard summarizes the key elements of the supplier selection, qualification, approval, management and control process, starting with determining when a new supplier is needed. The document then details requirements for supplier selection and control. Once a new supplier has been selected, the standard further outlines steps for supplier monitoring.

In particular, the standard encourages extensive communication between a company and a supplier and between a site and corporate leadership.

"There has to be transparency between the supplier and the client," said Schniepp.

One way to meet the requirements of the standard is to develop the role of a Chief Procurement Officer, or an individual responsible for ensuring compliance throughout the entire procurement process.

"You can never delegate accountability," emphasized VanTrieste. He went on to say that he hopes companies can use this standard to ensure quality in their procurement processes, leading to fewer recalls and warning letters.

"I think companies in general need to also get in sync with quality agreements," added Schniepp.

ANSI/PDA Standard 001-2020, Enhanced Purchasing Controls to Support the Bio-Pharmaceutical, Pharmaceutical, Medical Devices and Combination Products Industries can be purchased from the PDA Bookstore.

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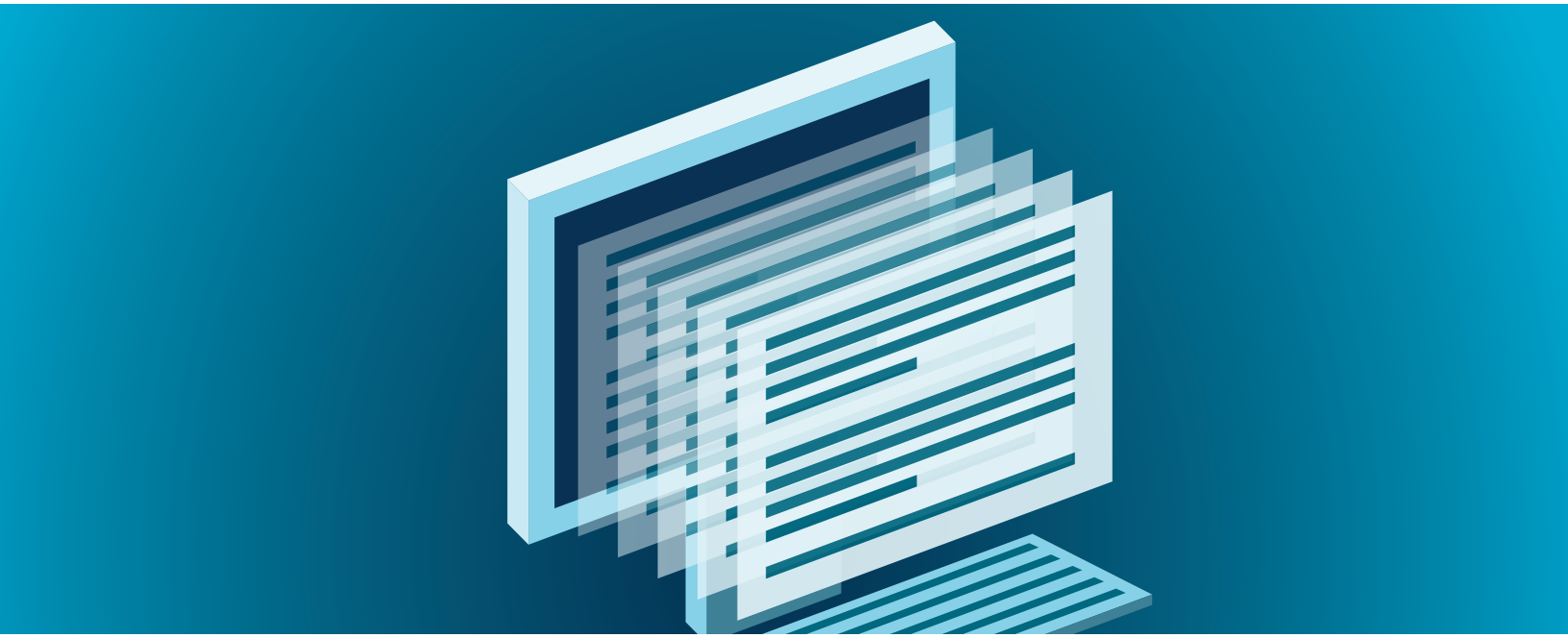
Regulator Develops Remote Inspection Process Due to Pandemic

Vladislav Shestakov, Russian State Institute of Drugs and Good Practices, and Elizabeth Meyers, Amgen



Russia's State Institute of Drugs and Good Practices (SID&GP) recently conducted its first remote GMP inspection of a manufacturing facility for an international pharmaceutical company. The "social distancing" restrictions in place due to Covid-19 limit the number of staff on site, necessitating the novel alternative. This article presents both sides of the experience to provide guidance for both manufacturers and regulators around the globe as they migrate to this new form of inspection ***(1).***

Many regulatory agencies have postponed or completely discontinued GMP inspections due to the COVID-19 pandemic ***(2–5).*** Alternative inspection practices have been proposed by both PIC/S and the U.S. FDA, using remote audits as an extraordinary interim measure during Covid-19 quarantines and travel restrictions ***(6,7).***

SID&GP quickly adapted to the current situation in order to avoid medicine shortages, proposing to temporarily conduct remote inspections of foreign pharmaceutical manufacturers. This approach involves a thorough review of submitted documentation and a risk assessment of the manufacturing site. The inspectorate's internal procedures were revised to include a detailed description of the inspection process based on the documents provided by the pharmaceutical manufacturer.

The SID&GP management must provide approval before a remote inspection can be conducted. Their decision to proceed is a risk-based approach, accounting for several factors including results of previous inspections, complexity of the site and criticality of products manufactured at the site. ***(7).*** For example, if a facility received a GMP certificate from a previous SID&GP inspection, the Agency could allow for a remote inspection that would even permit a new product to be included in a previously granted GMP certificate. If a previous inspection revealed critical findings, however, then a remote repeat inspection will include a thorough review of corrective actions, including revised documents, validation reports and proof of personnel training. The decision to conduct a remote inspection must be documented in the form of a protocol. Under this new approach, representatives of the manufacturing site to be inspected must also provide a written agreement to undergo the remote inspection.

To begin, 10 working days before the inspection, the SID&GP sends the foreign manufacturer a plan, including a list of documents that will be assessed. The manufacturer, usually through its Russian affiliate, forwards the requested documents in an agreed-upon form. Normally, paper copies of documents would be delivered to the SID&GP office by the Russian affiliate representative but, due

Read the authors' 2018 article, "Russian GMP Inspections Present Challenges, Opportunities: Part I," for more information about how the SID&GP was formed and how it performed its first GMP inspection. https://www.pda.org/pda-letter-portal/home/full-article/russian-gmp-inspections-present-challenges-opportunities-part-i

Many regulatory agencies have postponed or completely discontinued GMP inspections due to the COVID-19 pandemic

to restrictions caused by the pandemic, electronic copies are acceptable.

In general, requested information can be sent via email or by any other agreed-upon means. The best way to deliver the documents is to use a secured cloud storage solution restricted to specific participants and made available only during the inspection. Remote inspections require a different level of virtual security as documents are shared in their entirety, whereas during site inspections, the documents are just presented locally to inspectors. Extra time may be required for this should documents need to be translated, especially if translation of a large document must be completed within a defined timeframe. The inspection team will evaluate these documents and decide if follow-up will be required. If necessary, and agreed upon by both parties, a teleconference can be set up to answer questions. The inspectors may request additional documentation or information to clarify any questions that may have come up during the remote review.

Keep in mind that remote inspections inevitably take a longer than onsite inspections. This can be attributed to several factors, including different time zones and lack of direct real-time contact between inspectors and manufacturing site representatives. When the inspection format is changed to be remote, the inspection routine remains "classic," that is, the first day of the inspection opens with a presentation in English introducing SID&GP, the inspection team members and the purpose of the inspection. From there, the inspection follows the plan sent to the manufacturing site. On average, a remote inspection can take two to three times longer than an onsite inspection from start to finish, although there will be some breaks during the remote inspection as information is transferred and considered. Once an inspection has been completed, the team summarizes the potential findings and shares them with the Russian affiliate representative either through email or a close-out meeting via teleconference. The inspection concludes with a report, which is submitted to the applicant within 30 days, the timeframe established by Russian legislation.

A Site Perspective on Remote Inspections

For the manufacturer, it is very important to thoroughly prepare for a remote inspection. As with traditional onsite inspections, it is crucial to develop an integrated approach and to carefully coordinate work between the company's Russian affiliate office and the receiving manufacturing site. Quite frequently, international companies' manufacturing sites produce many product categories, destined for multiple countries. There could be instances where a manufacturing site has misinterpreted requirements of the Russian regulatory dossier, potentially leading to additional questions and findings by inspectors. Prior to an inspection, scheduling a teleconference between the hosting site and the Russian affiliate office is advisable. This will help the site to understand the content of a Regulatory Dossier as well as information within a Form 3, submitted before an inspection. Additionally, a host should have a clear understanding of a product flow beyond the manufacturing site, and a relationship between different legal entities involved in manufacturing, testing, release to market and distribution of a product in Russia.

During a remote inspection, it is necessary to establish an effective work pattern considering the different time zones involved and limited number of employees at the manufacturing facility due to the pandemic. The inspection support group should include not only the site's personnel, but also the Russian affiliate representative and the company's Quality groups to clarify local requirements and answer questions related to specific product flow or Analytical Normative Documents (AND). Russian affiliate representatives play a key role because there is no direct face-to-face contact between inspectors and a hosting site, and the affiliate representatives can serve as a "communication bridge" between a hosting site and inspection team. This representative should establish a positive working relationship with the inspectors. All requests and follow up questions must be submitted in Russian to the affiliate representative, who will then arrange for translation and then forward the questions to a hosting site.

An inspection manager within the hosting site should receive inspection requests and triage them to various Subject Matter Experts. After receiving the corresponding documents and/or records, an inspection manager may have to coordinate legal review and translation of documents. It is important to provide answers in an organized manner, e.g., accompanied by an explanatory letter linking each request to a corresponding response document. It is imperative to establish a mechanism to swiftly translate documents and cover letters. Since these steps can take some time, it is good practice to continue communication with the inspectors, so they know documents are being worked on and not ignored. The Russian affiliate representative can call an inspector to provide timelines and answer any questions.

A recent remote inspection showcases what Russian GMP inspectors might request for further clarification. After initial documents (see box below article) were reviewed by inspectors, follow up questions were asked to clarify which line is used to manufacture product under evaluation along with a request for an executed batch record. Additionally, inspectors requested a list of deviations and complaints related to the product, a list of GMP computerized systems used on the site and a cover page of an audit report for a contract manufacturing site. The initial list contained 31 requested items, followed by an ➤

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additional 23 questions. Five more queries were received after that. The inspection resulted in two minor findings.

Ultimately, SID&GP considers conducting remote inspections a contingency measure, undertaken only with respect to manufacturing sites subject to reinspection. On-site inspections will be resumed once the COVID-19 pandemic is over. SID&GP does not have a standard approach for all manufacturers requesting a remote GMP inspection. Before electing to conduct a remote inspection, SID&GP would study the drug master file carefully to assess the risk. For example, sterile manufacturing is a high-risk process and, most likely, SID&GP will likely not elect to conduct a remote inspection. From SID&GP's point of view, a remote inspection has a number of limitations. In order to reach an objective decision on a manufacturing site's compliance or noncompliance subject to GMP requirements via remote inspection, SID&GP will apply a comprehensive approach that has been developed during the COVID-19 pandemic.

The COVID-19 pandemic has put manufacturers, affiliates and inspectors in a new and challenging situation where it is in the public interest to continue to supply medicines while ensuring demonstrated compliance. Thankfully, recent examples of remote inspections show that, with good organization and coordination between the manufacturing site and Russian affiliate representatives, success is realistic and achievable.

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About the Authors

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Elizabeth Meyers is a Director of International and Distribution Quality at Amgen. Prior to joining Amgen, she worked as an analytical chemist in both the United States and Russia. For a number of years, she was a member of PDA's Regulatory Affairs and Quality Advisory Board.

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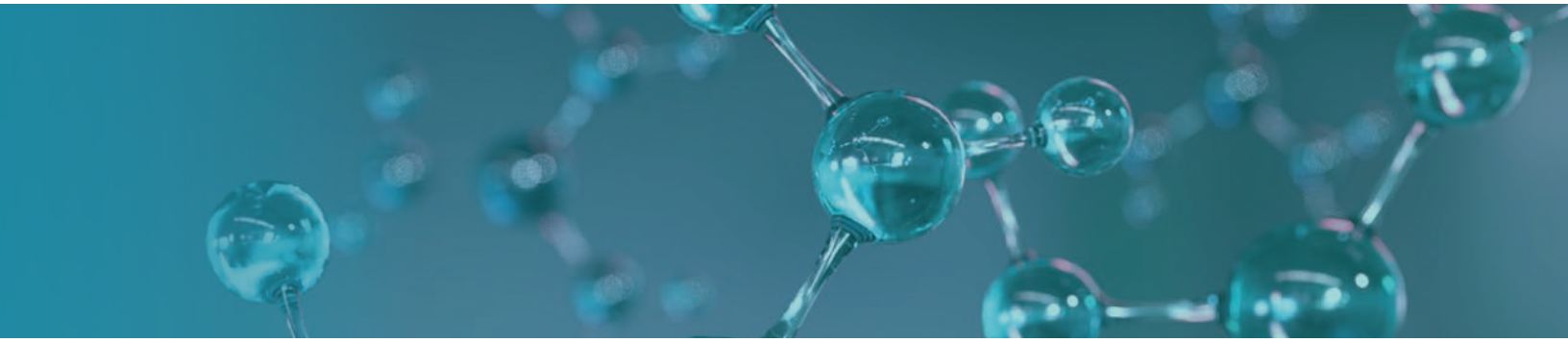

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The Use of Scientific Data to Assess and Control Risks Associated with Sterilizing Filtration

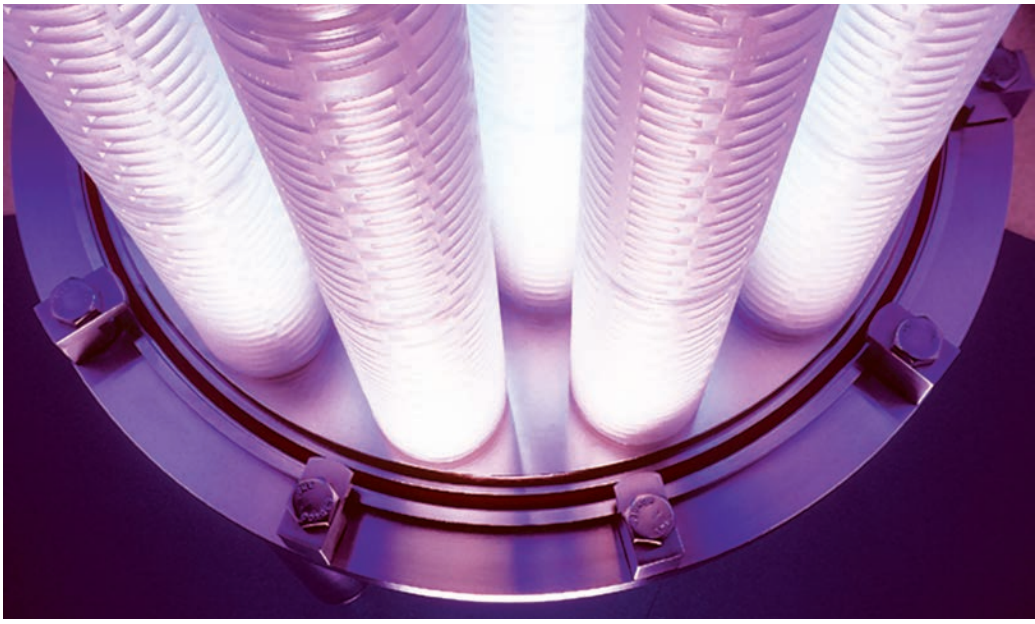
William Peterson, Merck & Co.

In recent years, a desire to minimize the risks associated with sterilizing filtration has prompted much discussion on the need for pre-use/post-sterilization integrity testing (PUPSIT) to detect nonintegral filters *before they are used* if there is any risk of not detecting them after the filtration process. This article aims to present guidance to industry (sterile drug manufacturers, filter suppliers and regulators) on how to develop and evaluate scientific data to prevent undetected non-integral sterilizing filters. Potential shortcomings of some previous discussions and publications on this topic are:

- Lack of published scientific data and evidence presenting relative risks and controls, thus leading to subjective evaluation of risk based on anecdotal information.
- Emphasis on detection of failures rather than prevention of failures.
- Use of biased risk assessments with predetermined outcomes.
- Efforts to eliminate *all* filter failure risk, ignoring additional risks posed by the addition of new control measures.
- Recommendation of a single means to control filter integrity risks for all products and conditions, without regard to process-specific differences in risk.

The underlying principle of the work described in this article is the use of objective scientific data to address these shortcomings, characterize risk, prevent sterile-filter failure, and ensure product sterility and patient safety.

This article draws conclusions from the scientific studies, workstreams, and publications delivered by the Sterile Filtration Quality Risk Management (SFQRM) consortium formed between BioPhorum and PDA. It uses those conclusions to provide guidance to industry on the use of quality risk management principles and scientific data to prevent undetected non-integral sterilizing filters.



PUPSIT was identified as a key topic in the mission statement of the SFQRM consortium: To explore the risk of product contamination as a result of sterile filtration failures, to identify the actions needed to prevent such failures (including the possible need to perform PUPSIT), to determine under what conditions it may be appropriate to deploy PUPSIT, and (in those cases) how to best perform PUPSIT.

It is generally recognized that **post-use** filter integrity testing is sufficient to detect filter failure and ensure patient safety, *unless there is a possibility that a filter passing the post-use test could have allowed bacterial penetration during filtration*. This possibility is the phenomenon referred to as filter "flaw-masking." This is hypothesized to occur when, for example, a filter is damaged during sterilization such that it allows bacterial penetration, but that the damage becomes plugged during the filtration process to such an extent that it allows the filter to exhibit a passing post-use integrity test result.

For this masking phenomenon to occur, two conditions must exist: First, there must be a flaw in the filter that is large enough to allow bacterial penetration during use, yet small enough to be plugged during the filtration process. Second, the product being filtered must be capable of blocking that flaw to the extent that it will pass a post-use integrity test.

Two workstreams within the SFQRM consortium were designed specifically to evaluate the risk of this filter flaw-masking and to understand in what conditions it might occur: Masking Studies and Bacterial Challenge Test (BCT) Data Mining.

Masking Studies

The objective of the Masking Studies workstream was to determine if the hypothesized masking phenomena can occur and, if so, under what conditions. The benefit of this information would be to provide industry with criteria for predicting and preventing flaw-masking.

To directly evaluate the possibility of filter flaw-masking, this workstream executed tests where worst-case, marginally flawed filters were challenged with a proteinaceous solution to plug the defects and create a passing post-use integrity test.

The consortium identified an additional way to evaluate the risk of flaw-masking that didn't require finding (or creating) defective filters

The following sets of flawed filters were used for the tests:

1. Cartridge filters rejected from filter manufacturing lines due to marginally out-of-specification integrity test results. Every sterilizing grade filter is integrity-tested within the supplier's manufacturing process as a release criterion. Over the course of time, rejected filters were collected for the masking trials. It should be noted that marginally out-of-specification filters are rare; most rejects are catastrophic failures (large defects that make the filters unable to be integrity tested). Therefore, it took multiple months to obtain the quantity used in these tests. Additionally, not all filters that fail the in-process integrity test will necessarily allow bacterial passage; in particular, marginal failures have a possibility of still being completely retentive.

2. Disc filters with intentionally created defects generated by laser-drilling 10 µm holes in 47 mm flat disc membranes. This set was included because of the difficulty in obtaining the marginally failed cartridge filters described above.

The results of these masking studies were shared in the article "Test Process and Results of Potential Masking of Sterilizing Grade Filters" ***(1).***

Of the 24 cartridge filters tested with 24 g/L foulant concentration and 90%+ flow decay (Set 1), only two demonstrated apparent flaw-masking with a pre-use integrity test **failure** followed by a post-use integrity **pass**. Interestingly, despite the high foulant concentration and flow decay, the majority of filters (19) experienced a *reduction* in bubble point after exposure to the foulant, while only five experienced a bubble point inflation (of which only two started out failing and ended up passing).

As for the intentionally damaged, laser-drilled filter discs (Set 2), an automated integrity tester was able to detect the damaged filters in all of the test conditions, whether challenged with 0.8 g/L or 24 g/L foulant solutions at any blockage level up to 75% (i.e., flow decay such that the final flow rate is one quarter or less of the initial flow rate). No flaw-masking could be identified when automated integrity testers were used, as all integrity tests failed the post-use test as well as the pre-use test.

At blockage levels above 75%, manual bubble point tests were performed, and only 2 of the 27 test conditions demonstrated passing post-use integrity test results. The two filters that passed the post-use test had high filter blockage levels of 81% and 97%–flow decay that is not typically experienced nor desired in commercial terminal sterilizing grade filtration applications where the filters are appropriately sized.

The results of the Masking Studies show that, while masking can be made to occur, it is not likely to occur under typical drug manufacturing conditions. These studies also demonstrate some criteria for evaluating the risk of masking: If companies manufacture products with unusually high foulant concentrations and use filters to levels that approach blockage conditions, then the risk of masking may be relevant. However, if filtration processes use systems that are appropriately sized, experience minimal flow decay and filter blockage, then the risk would be low and much less significant.

Bacterial Challenge Test Data

The consortium identified an additional way to evaluate the risk of flaw-masking that didn't require finding (or creating) defective filters. Any fluid with a clogging/

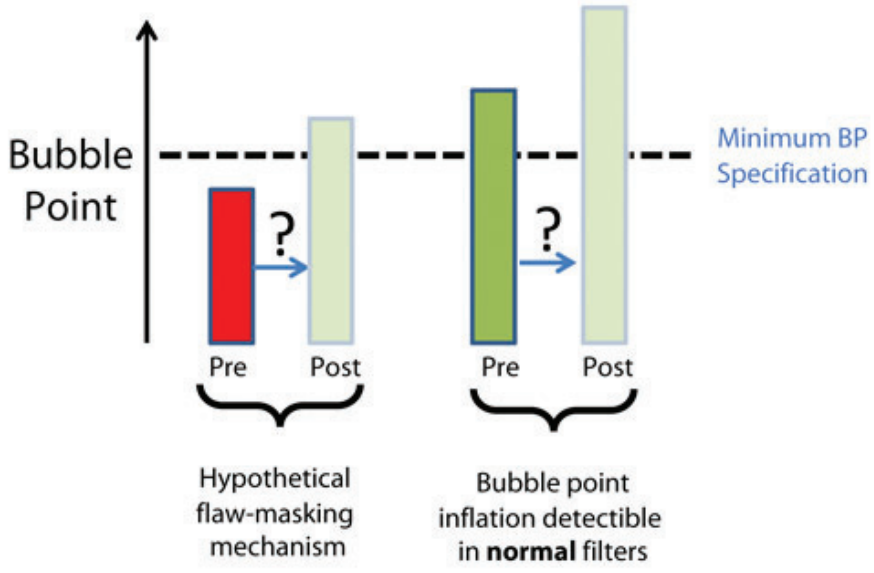


Figure 1 The mechanism of Flaw-Masking can be Identified as "bubble point inflation," even in integral filters

flaw-plugging mechanism (that is, would cause a flawed filter to appear integral in the post-use test) should also cause an increase in the bubble point value of an *integral* filter due to excessive pore plugging. In other words, the relative movement of a bubble point value between a pre-use test and a post-use test can indicate whether a flaw-masking fluid is present, even without the need of a flawed filter (**Figure 1**). The same concept applies for other integrity test methods correlated to bacterial retention, such as diffusive flow (i.e., flaw-masking with diffusion tests appears as a post-use diffusion rate *lower* than the pre-use diffusion rate). For the sake of simplicity, and because bubble point rather than diffusive flow data was available for most BCTs, bubble point will be used as the representative test in this discussion.

This led to the formation of the BCT Data Mining team whose objective was to *indirectly* evaluate the risk of filter flaw masking. This would allow the industry to better predict masking and implement controls to prevent it.

The BCT Data Mining team evaluated historical integrity test results from over 2,000 filters used in bacterial challenge tests, which was the bacterial retention validation performed on sterilizing filters according to *PDA Technical Report No. 26: (Revised 2008) Sterilizing Filtration of Liquids*. These historical tests provide two opportunities to evaluate whether a bubble point inflation mechanism (and thus a risk for flaw-masking) exists for any given fluid and filter combination:

1. The tests start with an initial confirmation of filter integrity (pre-use). Then the filters are exposed to the product, *plus* a high concentration of bacterial challenge organism (at least 10^7 CFU / cm^2 filtration area). This exposure is usually worst-case compared to the process being validated: longer filtration times, volumes and flow rates (thus representing a worst-case opportunity for filter fouling). The presence of the challenge organism further improves the data set: the cells and any cellular debris contribute an additional burden to the filter that could theoretically plug flaws or pores. After the completion of the test, the filtrate is evaluated for sterility, and the integrity of the filter is also checked (post-use). The SFQRM consortium recognized that historical test reports could be data-mined, comparing post-challenge integrity test results to pre-challenge integrity test results to determine whether a bubble point inflation mechanism exists for a particular filter/fluid combination.

2. In parallel with the bacterial challenge test of the sterilizing grade filters, a filter with larger pore size (usually 0.45 µm rated) is challenged as an experimental control to confirm that sufficiently small, viable and monodispersed bacterial cells are used and penetrate such a filter. This filter is also integrity-tested before and after challenge and will typically have a bubble point result well below that of a sterilizing grade (0.2 µm) filter due to the more-open pore structure. This 0.45 µm filter can be considered a model of a flawed sterilizing grade filter. Only if the 0.45 µm filter becomes so fouled that its post-use integrity test result exceeds the minimum passing result *for a sterilizing grade, 0.2 µm-rated filter* would flaw-masking be a risk for this model of a defective sterilizing filter.

The BCT Data Mining Team calculated a bubble point ratio by dividing the post-use integrity test result by the pre-use integrity test result and performed statistical evaluation of the results (post-use test results using a different wetting fluid from the pre-use integrity test were corrected through the use of conversion factors determined experimentally). A ratio above 1.0 represents bubble point inflation, and a ratio below 1.0 represents bubble point depression.

When the data were evaluated in aggregate, the mean ratio of the post-test bubble point to the pretest bubble point was exactly 1.00 (to 2 decimal places) for all test filters and 0.99 for all control filters (0.45 µm-rated filters) with narrow distributions around these means. This indicates that there is no wholesale trend of bubble point inflation in the industry, and the same was true when separately evaluating each filter membrane material, and each type of fluid (drug product, buffer, biologic, etc.)

When looking at individual fluid/filter combinations, the BCT Data Mining workstream determined that only a small fraction (less than 1.5%) of the filter test conditions demonstrated ratios above three standard deviations from the mean. These few outliers represent fluid/filter combinations with a theoretical possibility of a flaw-masking mechanism, at least when performed under the worst-case processing conditions and with the addition of the challenge organism. The trend identified by the Masking Studies team was confirmed here: flaw-masking or significant bubble point inflation is rare, and the few fluids with ratios notably above 1.0 tended to be those for which significant fouling (flow decay) was observed. The results of these studies were shared in the BCT article "Datamining To Determine The Influence Of Fluid Properties On The Integrity Test Values" ***(2).***

Evaluating the Risk of Flaw-Masking

It should be noted that the occasional possibility for bubble point inflation identified by the two workstreams does not represent a risk to product safety by itself. A bubble point inflation mechanism must be combined with the use of a flawed filter in the first place to create a risk of microbial contamination of the filtrate, followed by the theoretical flaw-masking. Not only must the filter be flawed, but it must be *marginally* flawed in such a way that a bubble point could still be obtained and inflated (atypical for the most common filter failure modes: catastrophic failures for which a bubble point is not obtainable due to membrane or capsule damage during shipping, handling or sterilization), yet sufficiently flawed to permit microbial passage. Typical use and sterilization of these filters are validated by the supplier and/or end user to remain integral under routine processing and sterilization conditions. It is important to note that, in order to maintain correlation of the integrity test with microbial retention for production samples tested in the course of routine filter manufacture, the filter manufacturer must eliminate all failure modes that are not detectable by a routine integrity test.

From the data presented here, it becomes clear that the majority of filter/fluid combinations present negligible risk of bubble ➤

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point inflation, and thus negligible risk of filter flaw-masking. Moreover, a review of terminal sterilizing grade filtration applications and their lack of excessive flow decay further minimize masking risks. If the sterility risk of flaw-masking were very remote, but there are no offsetting risks encountered by implementing and executing PUPSIT, then PUPSIT might be recommended in all cases. However, as was shown by two additional workstreams and consortium papers described in the next section, performing PUPSIT is not free from sterility risk itself. Instead, we find a *trade-off* of risks.

The difference between the two scenarios shown in **Figure 2** demonstrates why it is critical for end users to perform a robust evaluation of the risk of flaw-masking for their particular fluid and filter combination. The large majority of the processes where flaw-masking can be shown to *not* occur are represented by the scenario on the left, while processes with a significant risk of flaw-masking are represented on the right and may warrant implementation of PUPSIT or a more detailed evaluation of the relative risks.

Minimizing the Risks of Performing PUPSIT

Another workstream within the SFQRM consortium consisted of a team that executed detailed risk assessments of the entire sterilizing filter lifecycle as described in *Points to Consider for Risks associated with Sterilizing Grade Filters and Sterilizing Filtration (in-press)*. Although these were only examples designed to be used as templates for end users' process-specific assessments, they identified potential faults/failure modes that could compromise the integrity of a filter or otherwise add risk to the sterile product manufacturing process. Many of these potential failure modes occur during the execution of PUPSIT itself, which was confirmed by the results of a BioPhorum survey performed in 2019 by 21 drug manufacturing sites, representing 17 BioPhorum member companies.

The survey responses demonstrated that incorporating PUPSIT into a filtration process increases the complexity of the process and, with increased complexity, there are increased risks such as:

- Requiring the system to maintain much higher pressures, often exceeding 60 psi, increasing the risk of sterile boundary leaks especially when using single-use equipment. Deviations and leaks were reported in classified areas due to burst tubing junctions in such cases.
- Much longer process times associated with filter-wetting, blow-downs and the need to adapt to nonstandard situations (such as re-wetting the filter, re-orienting the filter to effectively remove air, etc.).
- System manipulations on the sterile side of the filter.
- Exponential increase in the complexity when using a redundant filtration design, if both filters need to be tested.

A similar survey performed in 2017 identified one drug product manufacturer that actually reported a process simulation (media fill) failure that was traced to a root-cause associated with performing PUPSIT.

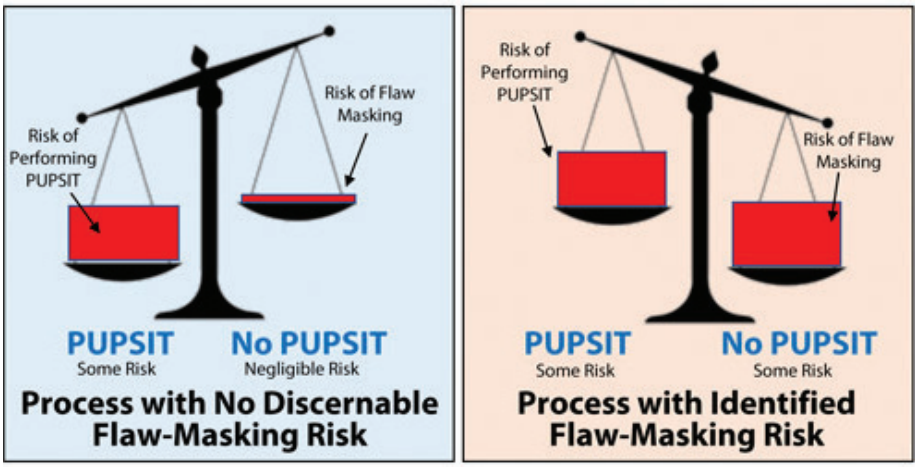

Figure 2 Two Scenarios

The message taken by the SFQRM consortium from the survey was that, with careful process design and development, filter users can mitigate (yet not completely eliminate) the increased complexity, product discard and turnover time associated with PUPSIT. It was with this in mind that the final deliverable of the SFQRM workstream was developed: *Points to Consider for Implementation of Pre-use Post-Sterilization Testing (PUPSIT) (in-press).*

This paper was designed to share PUPSIT best practices identified over the years by filtration subject matter experts at filter supplier firms and by end-users, so that when PUPSIT is performed, it is performed in such a way that it reduces the risk as much as possible (**Figure 3**). This also ensures that risk assessments are not biased: When comparing sterility risks of *not* performing PUPSIT with those encountered when performing PUPSIT, the PUPSIT case will be presented fairly, with as many best practices incorporated as possible to minimize the risks.

A reader of this comprehensive document will become intimately aware of the challenges of implementing PUPSIT, such as:

- Filter re-orientation
- Sterile blow-down after integrity test
- Performing PUPSIT on filters inside an isolator
- PUPSIT with redundant filters
- Addition of new sterilizing gas and liquid filters required to maintain the sterile boundary and allow PUPSIT (which must also be integrity-tested and represents additional possible failure points)
- Manipulations of the sterile side of the filter

Recommendation

Through the work of this team, the previously hypothetical flaw-masking phenomenon was shown to be at least theoretically possible through observation of masking on marginally failed filters and bubble point inflation, but only under extreme process conditions.

The data from the BCT Data Mining team and the Masking Studies team demonstrate that, for most of the fluid and filter combinations under normal process-

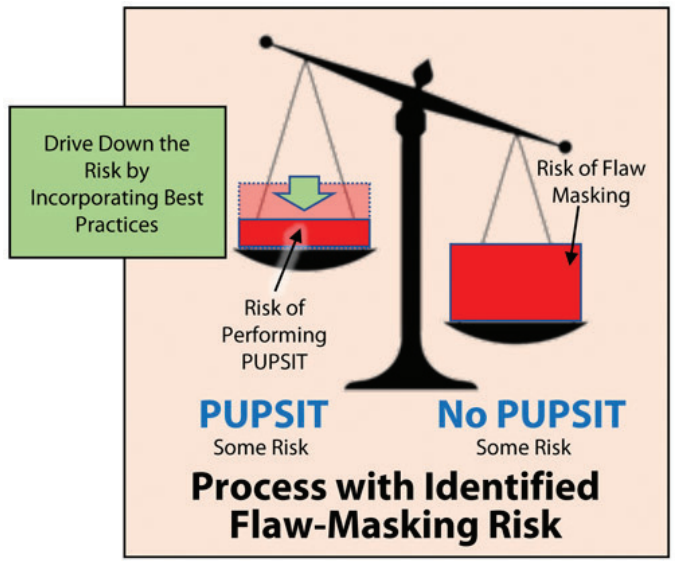

Figure 3 Best Practices to Drive Down Risk

ing conditions, there is no flaw-masking or bubble point inflation mechanism to pose a risk of a "false pass" post-use integrity test. This is especially true when considering the need of a sterilizing grade filter to be properly sized to filter the entire fluid batch at hand. This means such filters are typically over-sized and have enough capacity not to foul to a degree as experienced in the trial work. SFQRM team members, as experts in critical sterilizing filtration, shared the typical fouling levels encountered at terminal filters in their firms and reported that flow decays typically stay well below 40%. Based on this data, and the strong case for added process risk accompanying the performance of PUPSIT, we recommend that end users should take a risk-based approach to the implementation of PUPSIT in filtration processes.

Because the need for PUPSIT depends so strongly on the potential for flaw-masking, we recommend that any sterile product manufacturer considering a process *without* PUPSIT should perform a process-specific evaluation of the risk their fluid/filter combination has for flaw-masking. This may be as simple as a confirmation that the fluid components have no theoretical potential for flaw-masking (e.g., for final sterilizing filtration of WFI or some buffers), but a detailed evaluation may also include additional data such as:

- The level of flow decay (fouling percentage) encountered during the process
- Directly assessing their specific product's possibility to inflate the bubble point, either through BCT studies as shown in the BCT Data Mining paper, or through supplemental studies specifically designed to evaluate bubble point inflation
- The presence of pre-filtration or redundant filtration, which can remove flaw-masking components from the fluid stream before it encounters the final sterilizing filter (There is a strong rationale for never requiring PUPSIT for the downstream filter of a redundant pair.)

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- Use of laser-drilled flawed filter discs for the evaluation of filter flaw-masking

If there is a reasonable risk of flaw-masking that cannot be adequately reduced using process controls, the default position should be to perform PUPSIT. Any relative risk evaluation of "PUPSIT" and "No PUPSIT" process designs must ensure that the *best possible* PUPSIT scenario is compared to the No PUPSIT scenario, incorporating as many of the best practices identified in "Points to Consider for Implementation of Pre-Use Post-Sterilization Integrity Testing (PUPSIT)," (or practices providing equivalent reduction in risk) as possible.

This discussion focuses on the patient safety risk of releasing a non-sterile product. The observation herein is that, for the majority of cases, filter flaw-masking is not a concern; thus, post-use filter integrity testing is adequate. None of this discussion precludes a filter user from performing PUPSIT for other reasons, such as the business risk of processing with a non-integral filter that would not otherwise be detected until the batch is already filtered.

> **The Masking Studies can be used as a guide to determiner the likelihood that a given product may be prone to clogging a flawed filter**

Conclusion

Because product and processes may be unique, it is difficult to determine a single control measure that satisfies all situations. This paper and the referenced SFQRM consortium efforts are designed to provide the reader with guidance for the type of information to be considered to make an informed decision for their respective product and process.

The Masking Studies can be used as a guide to determiner the likelihood that a given product may be prone to clogging a flawed filter. The BCT Data Mining assessment of bubble point inflation provides further evidence that the likelihood is low. Both stand as examples of tests that can be performed by a parenteral drug manufacturer to evaluate the risk of flaw-masking in their process, and both can be used to provide guidance for precautions and controls that can be implemented to reduce or eliminate the likelihood of masking. Additional controls may include adding prefilters to reduce clogging materials, changing formulation parameters or conditions or the use of a properly designed PUPSIT procedure.

The example fault-tree analysis and risk assessments can provide guidance for the ➤

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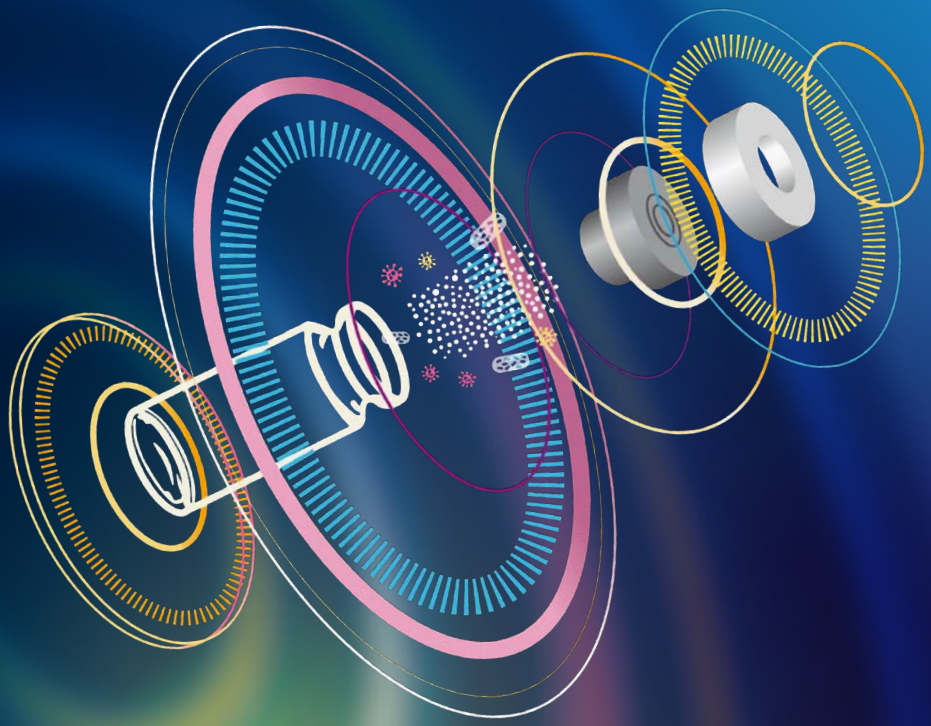

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likelihood of a filter becoming flawed during its manufacture, handling, transport and sterilization, as well as being a source of effective control measures. Assessments such as these can be used to identify any weakness in the process and help determine precautions and controls to reduce the likelihood of filter flaws and failures, as well as the adverse effect of these failures. Such precautions may include performing pre-sterilization integrity tests, adding prefilters to reduce clogging materials, changes in filter-handling procedures or packaging to reduce risk of filter flaws, changing sterilization process parameters or conditions and/or the use of a properly designed PUPSIT procedure.

The surveys, FMEA risk assessment and best practice points to consider provide insight into the complexity of properly designing and safely performing the PUPSIT procedure. It is essential that the reader understand the complexity of PUPSIT procedures. Any procedure performed during an aseptic process and on the downstream side of a sterilized system can be inherently risky and must be properly controlled. Once compromised, the chance of detecting a breach in a sterile pathway or aseptic process would be low and the result potentially catastrophic.

The question is not **whether** PUPSIT can uncover a pre-use, post-sterilization filter integrity failure, nor whether there is a theoretical possibility of a flawed filter passing an end-of-use integrity test, nor the impact of such an occurrence. The question is whether (and when) PUPSIT is the **best** choice to prevent such an occurrence from affecting product sterility. Once a company determines the combined risk of a filter becoming damaged and then having that damage masked, they can identify the steps that can be taken to reduce that risk and balance the residual risk to the risks of possible control measures.

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Appendix 1: Paradoxes of PUPSIT

During the consortium workstream meetings, technical discussions between the participants revealed two paradoxical cases where the very execution of PUPSIT presupposes an implicit risk-based approach to flaw-masking. These two points are presented below as examples of how risk-based approaches to filter flaw-masking are already being used in the industry, a prompt to consider whether similar assessments could be made that conclude that filter flaw-masking is not a risk.

Is a Product-Wetted PUPSIT Test Really "Pre-Use"?

There are two typical process designs for wetting out a filter in preparation for a PUPSIT test:

1. Wetting the filter with water, which often requires a blow-down step to dry the filter prior to filtration (to avoid dilution of the product)
2. Pre-wetting the filter with an initial flush of *the product itself*

Filter users have reported feedback from health authorities that Option 2 is preferred, since it does not require the challenging filter blow-down while maintaining sterility. However, one must consider Option 2 more closely: Imagine a filter that requires a 10 L flush with the product to assure complete wetting and reliable integrity-test results. Assume this example process has a 400 L total batch size. In this case, the process has already filtered 2.5% of the batch through the filter *prior* to executing the "Pre-Use" Post-Sterilization Integrity Test.

Might there not be components in the 10 L flush volume that could "mask" filter defects? The fact that this question is often ignored is an implicit acceptance of a risk-based approach to filter flaw-masking: The first 2.5% of the batch is unlikely to present such a fouling risk that a filter flaw could be masked. Is it not possible that, for other products, filtration of the full batch presents an equally low risk of filter flaw-masking?

Do Downstream Barrier Filters Need PUPSIT?

A common engineering control that enables the successful performance of PUPSIT is the use of additional sterilizing grade "barrier" filters downstream of the final product filter to maintain the sterile boundary. Hydrophobic barrier filters allow test gas to escape the downstream side without building up pressure. Hydrophilic barrier filters allow the filter flush and/or wetting fluid to be sent to waste while maintaining sterility of the downstream side. Occasionally, filter capsules with both hydrophobic and hydrophilic membranes are used to serve both functions.

When a hydrophilic filter is used in this application, it is serving the function of a *final sterile boundary liquid filter.* Would it not theoretically be subject to the same integrity-testing requirements of the main product filter, including the need for PUPSIT? The fact that this question is not frequently raised is another implicit acceptance of a risk-based approach to filter flaw-masking: The small volume of fluid passing through a hydrophilic barrier filter is unlikely to present such a fouling risk that a flaw in that filter could be masked. Is it not possible that the same risk-based approach could be taken for actual drug products that present an equally low risk of filter flaw-masking?

Global Regulatory Convergence Required to Expand Access to ATMPs

Rebecca Stauffer, PDA

Regulatory convergence will be key to ensuring access to life-saving therapies across the globe, according to U.S. FDA CBER Director **Peter Marks,** MD, PhD, in his presentation, "Moving Toward Global Regulatory Convergence for Advanced Therapy Medicinal Products (ATMPs)." Marks spoke in the final session of the PDA's *Advanced Therapy Medicinal Products* webinar series, which wrapped up on June 30.

"We would like to deliver safe and effective cell and gene therapies to those in need globally," he said. "So many people are suffering from serious diseases that could be helped by cell and gene therapies, particularly gene therapies, that it would be nice to have those developed and distributed not just in the high-income counties but also in the low- and middle-income countries. We believe that global regulatory convergence in high-income countries could help facilitate commercial availability and pave the way for the use of such therapies in low- and middle-income countries."

Regulatory challenges for ATMPs include the need to facilitate the manufacturing of safe ATMPs without being overly burdensome, achieving a balance between innovation and ensuring documentation of safety and efficacy, and keeping pace with rapid advances in the science and

technology of ATMPs. These challenges are common across the board globally, and regulators recognize that the existing regulatory framework is not ideal for these products.

While these challenges affect high-income countries, they are intensified within low- and middle-income countries, especially for gene therapies. Within these markets, the manufacturing of gene therapies faces further challenges—production of viral vectors can be inefficient and costly, purification procedures for gene therapies are complicated and not well understood and a concerted effort is required to produce and deliver them.

Marks said that FDA recognizes the need for global collaboration for gene therapies as the science is rapidly evolving while manufacturing innovation lags. Due to the intricate worldwide supply chain, improperly manufactured product could have disastrous consequences no matter where it is manufactured or administered.

He outlined some of CBER's regulatory convergence efforts. These include a proposed WHO white paper, regular meetings (virtual and otherwise) among high-income countries' regulatory bodies and encouraging sponsors to consider global development programs that allow FDA to invite other regulators to early-stage meetings.

"We really think that by taking a global approach, we can hopefully have gene and cell therapies come to bear improvement for serious disease in a variety of different settings in high-income counties but low- and middle-income countries as well," Marks concluded.

About the Expert

Peter Marks, MD, PhD, joined the FDA in 2012 as Deputy Center Director for CBER and became Center Director in January 2016.

For more perspectives on the manufacturing challenges of individualized therapies, read a summary of the opening talks at the FDA March workshop, *Facilitating End-to-End Development of Individualized Therapeutics.* https://tinyurl.com/y5qurkw4

Industry Must Move Away from Dye Ingress Test

Oliver Stauffer, PTI

Few events have contributed more to society's understanding of pharmaceutical container closure integrity (CCI) than the 1970 outbreak of bacterial infections from IV fluid container failure. Eight hospitals across seven states received compromised IV fluids, leading to nine deaths. The outbreak was eventually attributed to closure failure of IV fluid bottles during the sterilization process. The closure system failure was not something that would be detected with CCI protocols of that time.

While many aspects of pharmaceutical quality have evolved since the 1970 outbreak, dye ingress continues to be used to assess CCI with questionable value to patient safety. The draft Annex 1 and USP <1207> Container Closure Integrity Testing revisions show that regulators and pharmacopeias are looking for more improved and reliable methods for CCI testing.

Historically, CCI testing was performed using destructive probabilistic methods. Early drug delivery systems were basic, such as vials and ampoules. At the time, product classes typically consisted of small molecule applications. Methods such as the dye ingress test method would provide just enough functionality to address CCI risk for container and product characteristics of earlier parenteral treatments. The next generation of pharmaceutical treatments accounting for the majority of industry growth is already here, and they require new approaches to achieve modern quality assurances for patient safety.

More complex container types and large molecule biologics require a reassessment of what methods appropriately assure CCI for high-risk parenterals. The need for methods that improve on reliability, sensitivity and overall performance of methods is clear ***(1–3).*** Peer-reviewed research has shown the limitations of the dye ingress method in both sensitivity and reliability. Regulatory bodies have driven campaigns for automated data capture and data integrity, which runs counter to the basic aspects of a dye ingress test method. The industry has come to terms with the dye

ingress method as probabilistic in nature at a fundamental level. On many accounts, the dye ingress method falls short of providing effective CCI evaluation for high-risk parenteral applications.

To date, no peer-reviewed article supports effective performance and functionality of the dye ingress test method with actual product and "natural"-type container defects. Laser-drilled defects or thermal cracks are as close to naturally occurring defects that can be created for the purpose of validating a test method. Research using laser-drilled defects show performance deficiencies of dye ingress with water for injection as the container contents. If those same studies demonstrated performance of the dye ingress method with a medium mimicking large molecule products, the performance of the test method would deteriorate significantly.

Recent shifts within the industry acknowledge the importance of adopting newer deterministic technologies for the benefit of patient safety. For one, EMA's draft Annex 1 revision seeks 100% inspection on fused containers and appropriate quality test measures for applications based on level of risk. USP revamped USP <1207> to be prescriptive of deterministic technologies and encourage a deeper understanding of a container's CCI requirements. Industry-driven guidance documents are addressing the need for improved technology implementation into the pharmaceutical development and manufacturing space.

Patient care continues to be the primary mission of the industry, and simple compliance to achieve that objective is not enough. The U.S. FDA continues to encourage a "quality culture" agenda versus a "compliance culture," driving industry to look at quality more holistically. Regulatory bodies have been explicitly targeting container performance, data integrity and systems put in place to support quality. Every regulatory and guidance body is moving toward more reliable and accurate test methods. CCI testing is not meant to be viewed as just a method of compliance to regulatory guidelines, its true purpose is to ensure patient safety by verifying container quality.

The dye ingress test is by no means extinct. There are benefits and upsides to the application of the method. All supporting evidence, however, suggests that maintaining the use of dye ingress for parenterals is counter to assuring patient safety. The use of dye ingress could be justified under certain circumstances where other deterministic technologies fail to perform. Those circumstances are almost nonexistent within parenteral applications. Newer leak detection technologies outpace the dye ingress method in practicality, sensitivity and reliability.

For most parenteral applications, there are multiple deterministic CCI test methods that improve on the probabilistic predecessors. Newer technologies are nonsubjective, can be calibrated against known standards, provide the ability to automatically record data and are sensitive to defects that present critical risk to ➤

patients. At the very foundation of quality, newer methods are being adopted based on the ability to assure CCI for new container formats and product classes where traditional methods clearly fall short.

Container performance and integrity testing was simpler in a small molecule world with few container presentations. The pharmaceutical industry continues to develop new containers to bring treatments to market. It is a choice to continue reliance on the dye ingress test method for CCI, but that choice must reconcile with current products and delivery systems. To date, the overwhelming majority of peer-reviewed research lays out a path away from the dye ingress method. Pursuing the quality solutions of the future means the same level of scientific understanding must be applied to the selection of deterministic technologies. It is clear that a challenge exists—pharmaceutical containers and closure systems have quickly outpaced traditional CCI test methods. Implementing a modern alternative that can adapt and evolve alongside the industry to serve its primary purpose of patient care is the optimal solution.

> **The pharmaceutical industry continues to develop new containers to bring treatments to market**

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About the Author

Oliver Stauffer joined PTI in 2005 as a member of the research and development team working on nondestructive testing of high-risk pharmaceutical packaging. During his time with PTI, he has developed several technology platforms, measurement methodologies and technology patents. In 2016, he was appointed CEO.

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Masahiro Akimoto

PDA Continues Global Expansion

As a member of PDA's Board of Directors, I am honored to be part of the team that helped organize the inaugural Asia-Pacific edition of the *PDA Letter* earlier this year.

In 2006, PDA opened its first office outside the United States in Berlin. Today, 14 years later, our activities in Europe have grown. Last year, PDA opened its second overseas office, PDA Asia Pacific, in Singapore.

PDA recognizes the need for high-quality technical resources in the Asia-Pacific region and, through the Singapore office and regional chapters, it is looking to expand our conference offerings. Of course, there have been changes in light of the COVID-19 pandemic. Chapters, in particular, the Singapore Chapter, have risen to the occasion by offering virtual events.

In the fall, two conferences are scheduled: the *2020 PDA Asia Pacific Pharmaceutical Manufacturing and Quality* conference, Sept. 22–23, in Singapore, and the *2020 PDA Asia Pacific Conference,* Oct. 12–13, in Incheon, South Korea. I recommend that you check the PDA website for updates in the event that there are changes due to the pandemic.

In addition, PDA is moving forward with translating our technical documents, including our technical reports, into local languages.

This is a lot of work and the novel coronavirus is impacting the pharma industry worldwide. PDA will need volunteers to assist in these efforts, from helping with translations to speaking at conferences. If you are interested in volunteering, you can help at the local level through your chapter (https://www.pda.org/pda-chapters) or by contacting PDA's Volunteer Coordinator (volunteer@pda.org).

This is a challenging time around the world and we can achieve great things by working together.

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