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PDA Letter

Volume LII • Issue 4 www.pda.org/pdaletter April 2016

Virus Retentive Filtration in Biopharmaceutical Manufacturing 20

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Validation of Lyophilization (May 11-12)

Learn the requirements for qualification of a lyophilizer and validation of lyophilization processes. Bring any questions and real-life issues related to lyophilization you would like to discuss! At the completion of this course, you will be able to explain the impact and limitations of analytical methods used to evaluate lyophilized materials.

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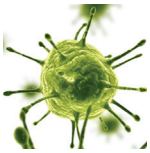

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PDA Board of Directors Nominations Wanted

PDA members can nominate candidates for four open Director positions on the Board of Directors for the 2017–2019 term.

"We do not want to miss outstanding members of our organization and strive for a diverse Board of Directors," says **Hal Baseman,** the current Nominating Committee Chair and Immediate Past Chair of PDA.

All PDA members are encouraged to nominate their peers within the Association for the Board of Directors election, although certain prerequisites are necessary. For example, only members in good standing can nominate and be nominated (that is, their membership is current). All nominations will be considered and evaluated according to the following criteria: 1) status of membership; 2) level of activity within PDA; 3) volunteer history; and 4) diversity of representation.

"When you nominate a candidate, please be so kind as to include a brief explanation, which makes it easier for the selection committee to make their final choice," requests Baseman.

To nominate, send an email to: nominate@pda.org. Nominations for the 2017 Board of Directors elections will be accepted through April 22, 2016.

Former members of the Board of Directors pose at the *2011 PDA/FDA Joint Regulatory Conference*

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Revived Kilmer Conference to Explore New Landscape

Joyce Hansen, Johnson & Johnson

Think back to 1976, if you were around then.

That year, the year of the first *Kilmer Conference,* clothes were polyester, music was vinyl, and "CC" involved actual carbon. If you worked in sterility assurance, you probably had few avenues for sharing knowledge or conferring with colleagues outside your organization.

The *Kilmer Conference*—named for Johnson & Johnson sterility assurance pioneer **Fred Kilmer,** and revived for 2016—helped to change all that.

How Kilmer Made Us Who We Are

Over the past 40 years, the *Kilmer Conference* helped forge a community, solidified professional knowledge, and played a formative role in many participants' careers, mine included. At my first *Kilmer Conference*—and no, I won't reveal the year—I met leaders who helped me grow as a professional by sharing their experience in the field.

Of course, the world has changed significantly over the past four decades, and so has the sterility assurance community. Even in the years since 2003, when the last *Kilmer Conference* was held, we've seen dramatic changes. The world felt less connected in the early 2000s. There was email, but it was still the era of flip phones. We had less opportunity to communicate with global colleagues. But the world is smaller today—more connected. In sterility assurance, we've gone from having national standards in each country to having international standards—the culmination of a process that began at the end of the '90s.

Kilmer Shaping the Future of Sterility

Fast forward to 2016. The revived *Kilmer Conference* is as important as ever, especially as we adapt our methods to an ever-increasing rate of innovation. What used to take 5–10 years, can now take 18–24 months, an acceleration that has forced us to identify new and innovative ways to obtain the information necessary for validation, in order to ensure more efficient delivery of new drugs and devices to patients.

The faster pace of innovation places new demands on our profession. This means we need to think in advance about sterilization methodologies and processes for products that lie beyond the horizon. Already, biologics and personalized medicines pose unprecedented challenges. For example, how will we respond when the active ingredient cannot be aseptically processed or terminally sterilized?

Increasing our ability to proactively adapt to innovation is one of the goals for the 2016 *Kilmer Conference.* As I see it, this means becoming stronger in five core areas: competency, community, connection, career and collaboration. Let me explain what each one means.

Competency: The *Kilmer Conference* brings together leaders from the medical device and pharmaceutical industries, from regulatory agencies and academia, from contract sterilizers and contract laboratories, and from clinical staff and hospital central supply. This diverse professional mix helps us better understand the technical needs of our interwoven community.

Community: The conference brings participants together to consider what we need as a field. It gives us a chance to tackle common challenges together despite working in different industries. It reminds us what we have in common.

Connection: It strengthens our "connections" as a community, but I also want us to consider our "connection" in another sense. I hope we'll use the digital tools at our disposal to stay in close contact with colleagues to discuss challenges, pose questions and exchange ideas.

Career: The *Kilmer Conference* is fundamentally about knowledge sharing and professional development. My advice to anyone attending their first *Kilmer Conference* is to talk to as many colleagues as you can, and use the breadth of topics to step outside your comfort zone. Seize the opportunity to better understand how the work you do fits into the larger mission of our community.

Collaboration: Finally, this conference should encourage us to become more collaborative, not just with one another, but with our suppliers and external manufacturers. With them, we need to find ways to meet the challenges of the future—including, to name one, an increase in combination products and other products that require multiple companies working together. Finding ways to sterilize such products will enable healthcare professionals to deliver safer medical care to patients.

With the revival of the *Kilmer Conference* in 2016, we're recognizing a heritage of innovation. The *Kilmer Conference* proceedings, now available through the Association for the Advancement of Medical Instrumentation, are an archive of milestone advancements, like parametric release, first presented at Kilmer. But as we nod to the past, we're building the future of sterility assurance. I'm confident that in 2016 and beyond, the *Kilmer Conference* will be even better than before. We're connected. We're international. And around the world, we have a common language—not English, but sterility assurance.

PDA Volunteer Spotlight

Dipti Gulati, PhD

- President
- *PJI Biotech*
- Member Since | 2008
- Current City | Morrisville, North Carolina
- Originally From | New Delhi, India

PDA has encouraged me to think outside the box

Dipti used to perform skits on stage in university

What have been your favorite activities as a PDA volunteer?

As a volunteer, I enjoyed participating as a member of the team providing comments on the U.S. FDA quality metrics guidance. In addition, I enjoy engaging in discussions as a member of the Quality Systems and Quality Risk Managment Interest Groups.

Why did you join PDA?

I joined PDA to expand my knowledge on pharmaceutical regulations and stay current on industry trends.

What upcoming PDA conference are you excited about?

I am looking forward to the *PDA/FDA Joint Regulatory Conference.* I have been attending this conference since 2008 and like that it has a great mix of representatives from both industry and regulatory agencies.

What topics should the industry be talking about?

I think FDASIA and biosimilars are two hot topics with important implications for the future. Both of these are developing areas; more work is needed from regulators as well as from industry.

How did you get to where you are now in your career?

I started my career as a biopharmaceutical process and analytical development scientist. Over time, I felt that in addition to the science, quality is also essential to delivering high-value products to patients. Therefore, I moved into quality management. My current focus is the global side of quality management.

What would you tell someone who is entering the industry?

Join PDA as soon as you can so you can quickly learn more about the industry and its regulations.

What was your dream career as a child?

I wanted to be a medical doctor.

What do you enjoy doing in your spare time?

Reading, cooking, skating and painting

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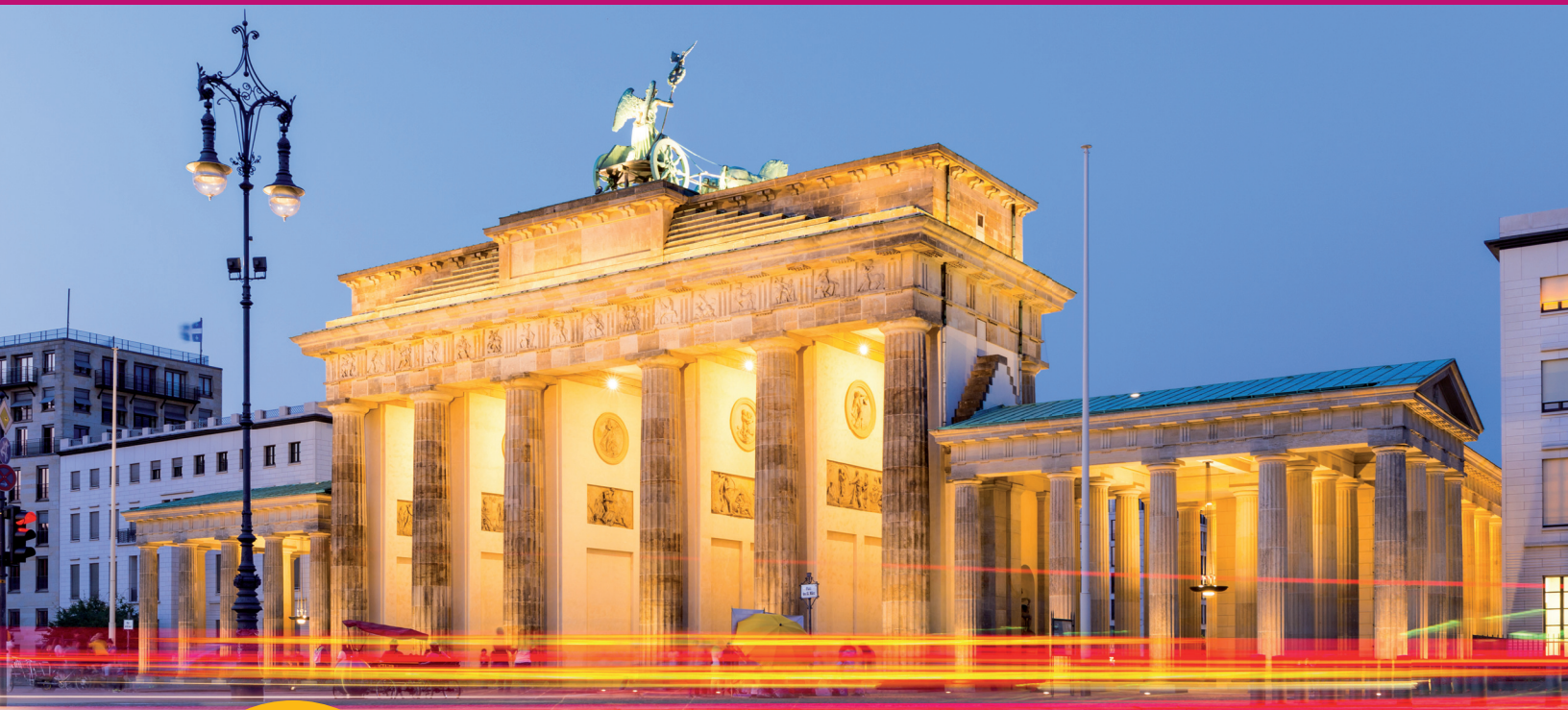

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chapter update

Quality by Design Also Applicable to Legacy Products

Robert Sullivan, Committee Member, Australia Chapter

What does Quality by Design (QbD) mean for legacy products? What are the minimum requirements? And how do legacy products fit in with the "design space" concept?

PDA's Australia Chapter explored these questions at its successful, "Quality by Design for Legacy Products" event last October. Three speakers from different backgrounds, **Gary Warren, Jonathan Parks** and **Sonja Cuce,** offered varying perspectives for attendees.

Warren began by providing an overview of the core definitions related to QbD and its objective—increasing product and process understanding in order to minimize patient risk. Achieving this requires consistency of product and process performance. He also explained that QbD must be a multifunctional exercise, and not just a quality activity.

Next, Warren described the key documents comprising the QbD "infrastructure:" Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA) and Control Strategy Summary (CSS). Definition of the QTPP enables the CQA to be defined, subsequently enabling development of the process control strategy. In performing QbD, another key document is a matrix of CQA and process parameters, enabling companies to identify intersection points on which to focus control.

(l-r) Eoin Hanley, PDA Australia Chapter Membership Liaison Officer, Gary Warren, Jonathan Parks, and Sonja Cuce

Parks reinforced Warren's definitions and also discussed the process flow for key activities and documents. He spent some time discussing the "Design Space" concept. Movement of process parameters within that formalized space is not "change" as historically defined and controlled for within pharma. He also stressed the importance of establishing a control strategy once the design space has been established, followed by Product Lifecycle Management through continuous evaluation of process and product performance and improvement opportunities.

For legacy products, there is a wealth of historical data available from multiple sources. In fact, a major challenge concerns accessing, assessing and making sense of it all in order to create the key elements of QbD. Parks then described a completed QbD for Ventolin (salbutamol/albuterol) Nebules Solution, a 25-year-old sterile, nonpreserved asthma rescue medication packaged in a blow/fill/seal container. Identifying the CQAs required referring to the relevant regulatory standards and guidelines for inhaled products. Again, a critical document was the matrix of CQA along with process parameters highlighting main areas of focus for control.

Cuce then looked at the regulatory aspects of QbD for legacy products, including a definition of "legacy product." In Australia, products are considered "legacy products" when it has typically been more than 15 years since registration; the older examples of these products may have had minimal documentation of pharmaceutical development or validation. In her view, successful QbD implementation entails involving Regulatory Affairs very early in the scoping process, implementing needed changes and a willingness to engage with regulators on matters of sufficient importance.

A lively Q&A session followed these presentations. An attendee expressed concerns about the resource requirements of performing QbD for legacy products. Parks admitted that it is a very resource-hungry process. A typical manufacturing site can only manage one product at a time, making prioritization critical. Another concern raised was the challenge of getting contract manufacturers to perform QbD—this remains an open question with few concrete answers.

All in all, attendees took away the importance of factoring in QbD when working with legacy products thanks to the three speakers.

PDA Who's Who

Sonja Cuce, Principal Regulatory Consultant, Belsyme Consulting

Jonathan Parks, Technical Project Leader, GlaxoSmithKline Australia

Gary Warren, Director of Haemostasis and Thrombosis R&D, CSL Behring

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Bridging the Generation Gap with New Hires

Three Steps for Getting the Most from Millennials

Kate Zabriskie, Business Training Works

"DID YOU SEE *what she wore to work today? What was she thinking? This is a corporation, not a club!" "How does he not know to bring a notebook and a pen to a meeting? Do I have to tell him everything?" "What would make her think it was okay to party with the clients until three in the morning? Does this woman have no understanding of boundaries?" "Did you know his mother called HR to find out when he would be getting a raise? Unbelievable!"*

If you have new hires fresh out of school in your workplace, some of that may have a familiar ring.

So what's happening? Are the new hires prompting those reactions just bad hires? Are you just unlucky? Probably not.

Rather, the source of these surprises most likely has to do with training (or the lack of training) related to workplace expectations. Before you say "but they should know," don't waste your breath. Maybe they should know, but they don't. New hires are called new hires for a reason. They are freshly minted employees who don't know much about the workplace because most of them haven't been in it that long.

Think about it. If the shoe were on the other foot and you found yourself in some kind of *Freaky Friday* hell, do you think you would flawlessly understand today's high school or college social codes? Dream on and good luck with that.

As someone with more experience than the people you hire, you have a responsibility to get them off to a good start. By consistently following three steps, you can short circuit many of the problems people encounter when they start working with new hires.

Step 1 Understand Something About Them

Millennials as a generation are different from those who have come before them. More than a few still live at home and don't plan on leaving soon. Besides, if they borrowed money for school, they may already owe as much as what amounts to a mortgage. That doesn't mean they're clueless about life outside of the nest, but their circumstances are probably very different from yours at the same age. Assume nothing.

Next, you must understand these people grew up surrounded by ever-present technology and in an era of instant answers. Sure, you may have had an Atari or Nintendo, but it's not the same thing. They had—and still have—Google. They are used to being able to find information quickly. Raised in an era of parents as friends and instant answers, many of these individuals have no problem questioning authority. In the workplace, you may see a new hire ask questions and interact with senior leaders in ways you don't expect.

Another difference between Millennials and other generations is how they view praise. As children, this generation of people played on sports teams where everyone received a trophy just for showing up. They were also rewarded and recognized with ribbons and certificates at school for being polite, having integrity and displaying common courtesy. Millennials expect feedback larded with praise whether merited or not.

Longevity in an organization is another difference between this generation and others. Years ago, it was a major taboo to job hop or have gaps on a resume. These days, you will find that this generation will gladly take six months off to go hiking along the Appalachian Trail or volunteering somewhere overseas. Strangers to delayed gratification, they aren't saving those activities for retirement, and they don't expect to spend a lifetime with a company. Instead of pretending that Millennials will be part of your team for a decade or more, look for ways to make the most of the time you have together with them.

Step 2 Spell Out Everything

Millennials are not mindreaders. Do not rely on their clairvoyant powers. Most of them don't have any.

Again, assume nothing. Take workplace dress, for example. There was a time not too long ago when women wore hose to work and wouldn't consider crossing the office threshold in open-toed shoes. That was then. These days, if you offer no guidance, some will cross the threshold in footwear you wouldn't wear outside your house. And when the parade of fashion crimes starts, you will have no one to blame but yourself. You may need to tell people that contrary to what they may see online or in a magazine, the flip-flop is not the new dress shoe.

Once you've thought about the basics, you'll need to anticipate the times "on the job" when the new hire will interact with people outside your organization. Is the new hire attending a client function with you? If so, it makes sense to review your expectations before you head out the door. Whereas most people might do fine on their own, that's not the point. If you expect a certain set of behaviors, you need to make clear what they are.

Spelling out expectations for employee behavior and dress down to the last detail will help Millennials acclimate better to your organization

Step 3 Use Praise Often

Most people like praise. As mentioned earlier, the difference between Millennials other generations is that they are used to getting it.

To get the most out of your new hires, you must learn how to give feedback more often. A word of caution: Millennials know when they are being patronized just as well as the next person, so choose your words wisely. At this point, a lot of them will have figured out that the trophy thing wasn't such a hot idea. Instead, you are going to have to pay attention and recognize good work. It's more time consuming, but if you put in the effort, you will probably see more of what you want to see.

Do not rely solely on feedback on the fly. The reality is it's easy to get busy. Make the time to have structured conversations with your new hires about their development. Thinking about skipping this step? Don't. Regularly scheduled one-on-one meetings will ultimately benefit the new hire, the organization, and you.

A Final Thought

Developing any employee takes time, and working with new hires has its own set of challenges. There are few shortcuts along the road to success in the workplace.

How much effort you put in to another person is certainly up to you. But think back to your first days in the world of work. If someone spent the time to work with you early in your career, you were lucky. If you didn't have that opportunity, don't you wish you had?

About the Author

Kate Zabriskie is the president of Business Training Works, Inc., a Maryland-based talent development firm. She and her team help businesses establish customer service strategies and train their staff effectively.

snapshot

Virus Topics Among Top 50 Most-Read PDA Journal Articles

Biopharmaceutical production is one of the fastest growing fields within the pharma industry. Viral contamination is a big concern for those involved in this area due to the use of cells derived from living organisms. Not surprisingly, six of the Top 50 most-read articles in the *PDA Journal of Pharmaceutical Science and Technology* for February explore the latest developments in this area, including proceedings from a number of virus-oriented symposiums and meetings PDA has participated in.

Below are brief synopses of these articles, which can be accessed at the PDA journal website (journal.pda.org).

Lixin Xu, et al. "Role of Risk Assessments in Viral Safety: An FDA Perspective" (January/February 2014)
Viral contamination is a risk inherent for all biotechnology products derived from cell lines. Due to the complexity of viral contamination, which can occur at the raw material level or during production, systematic risk assessments are needed. A model failure mode and effects analysis (FMEA) approach allows for more effective assessment of risk in the production process, particularly as viral contamination can occur at different points during the product lifecycle.

George Miesegaes, "Viral Clearance by Traditional Operations With Significant Knowledge Gaps (Session II): Cation Exchange Chromatography (CEX) and Detergent Inactivation" (January/February 2014)
Presentations by Amgen and Novartis representatives at the 2009 Viral Clearance Symposium explored the use of cation exchange chromatography (CEX) as a mechanism of viral clearance. While both studies presented interesting data, additional research is required to fully understand the nature of CEX for viral clearance.

Arifa S. Khan and Dominick A. Vacante, "Introduction and Workshop Summary: Advanced Technologies for Virus Detection in the Evaluation of Biologicals—Applications and Challenges" (November/December 2014)
The November 2013 workshop, *PDA/FDA Advanced Technologies for Virus Detection in the Evaluation of Biologicals—Applications and Challenges,* offered an opportunity for open dialogue between industry and regulators based upon data-driven presentations and discussions on the use of advanced virus detection technologies. While new technologies in this space offer the potential to significantly reduce contamination risks, there remain significant challenges.

David Roush, Kurt Brorson, and Rich Levy, "Proceedings of the 2013 Viral Clearance Symposium (Princeton, NJ)" (January/February 2015)
The third *Viral Clearance Symposium* offered an opportunity to follow-up on topics raised at the second symposium as well as address new topics such as novel approaches to viral clearance and implementation of an integrated adventitious agent control strategy to link upstream and downstream processes.

Johannes Blümel, "Viral Safety Perspective from the Paul-Ehrlich-Institut in Europe" (January/February 2014)
In 2008, EMA released a guideline covering viral safety evaluation of biotech investigational medicinal products, defining the basic principles on data requirements for viral safety. EMA's aim is " to design steps to clear a wide range of different viruses in order to cover undetected, unexpected, or unknown emerging viral contaminants," an area in which the Paul-Ehrlich-Institut in Germany is heavily involved.

"Organizers and Participants of the 2011 South San Francisco Viral Clearance Symposium" (January/February 2014)
Find out the names of those involved in the organizing committee behind the second *Viral Clearance Symposium*. Participants, representing a wide range of segments of the industry as well as global regulatory bodies, are also listed.

Additionally, the organizers responsible for last year's *Virus and TSE Safety Forum* in Lisbon have submitted a synopsis of that meeting to the *PDA Journal of Pharmaceutical Science and Technology;* look for it shortly in the "Accepted Papers" section of the website.

Best Practices for Leachables Under Development

BPOG Disposables Team Moves Forward

A recent *PDA Letter* article ("Survey of Industry Leachables Best Practices Completed," March 2016) provided results from a BioPhorum Operations Group (BPOG) survey of member companies' current practices for conducting leachables studies. Based on these results, the team responsible for the study plans to develop a document outlining best practices for leachables studies with the hope that such a document will encourage greater use of disposable components (for simplicity, the term "disposables" is used in place of "single-use systems" below).

The first step in the direction of a best practices document requires an understanding of the definitions of "extractables" and "leachables." While both terms have been used synonymously, there is a clear difference between the two. Definitions for both, taken from USP <1663> *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery. Systems* and <1664> *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems,* offer some insights.

"Extractables" are organic and inorganic chemical entities that can be released from a test article and into an extraction solvent under laboratory conditions. Test articles include packaging systems, delivery systems, manufacturing suites and/or their associated materials or components of construction. Depending on the specific purpose of the extraction study, these laboratory conditions (e.g., solvent, temperature, surface area-to-volume ratio, etc.) may accelerate or exaggerate the normal conditions of storage and use for a packaged dosage form or during manufacturing. Extractables themselves, or substances derived from extractables, have the potential to leach into a drug product under normal conditions of storage and use and become leachables. Thus, extractables are potential leachables.

"Leachables" are foreign organic and inorganic chemical entities that can seep into the finished drug product from several potential sources, such as the finished drug product's manufacturing suite, packaging or delivery system and/or their components, and construction materials under normal manufacturing conditions, storage and use. Since leachables are derived from these sources, they are not related to either the drug product itself, its vehicle or ingredients.

Chemical compounds that actually migrate from or through the contact material into the process stream under normal manufacturing/storage conditions are referred to as "in-process leachables." If these cannot be cleared or diluted to an undetectable level in the final drug product, the in-process leachables will also be known as leachables.

Both categories of leachables are typically a subset of extractables, or are derived from extractables. Herein, the term "leachables" will embrace both types.

Lack of Literature on Leachables

Last year's annual survey from BioPlan Associates showed that respondents' concerns about extractables and leachables remains the No. 1 hurdle preventing many from implementing disposables ***(1).*** This response has been consistent throughout the previous six years of the BioPlan survey.

In spite of this concern, presentations and publications on leachables are rare, compared to content on extractables developed by both component suppliers and end users. Leachables testing is usually the responsibility of end users; it is often difficult due to the complexity of biological drug product matrix.

Since no standard extractables test protocol is available, disposables suppliers have been conducting extractables studies based on adaptations of the well-known Product Quality Research Institute (PQRI) leachables and extractables recommendation for inhalation products ***(2).*** The lack of specificity in the PQRI approach for disposables, however, has led to challenges for both suppliers and end users when adopting its methodology for study designs. Since various study designs are based on supplier interpretation of methodology, it is difficult to compare results from different suppliers for similar components during the selection phase. Subsequently, end users often have to perform further extractables studies, such as looking at additional relevant solvents and timepoints to bracket user process matrix and conditions. Not only does this slow down the selection of disposables, it also yields unnecessary and redundant studies of the same disposable by numerous end users.

Several organizations have since developed recommendations for developing a standard extractables protocol, among them PDA, BPOG, and the Bio-Process Systems Alliance (BPSA). The objective of the BPOG survey of member companies was to ensure an acceptable standard for risk assessment and testing of leachables through a best practices guidance document.

Following review of the survey as well as analysis of current regulatory trends at the subteam's workshop, the subteam identified three key areas that must be addressed in a best practices document.

3 Areas of Focus for Leachables

1. Consistent and User-Friendly Risk Assessment Model and Process: Risk management principles are effectively utilized in many areas of business and government, including pharma. Risk is defined as the combination of the probability of occurrence of harm and the severity of that harm. Protection of

patients by managing risk to product quality of the drugs manufactured is of utmost importance. Drug product manufactured using disposables necessitates some degree of risk due to potential of leachables from disposable components.

Quality Risk Management (QRM) is a systematic process for the assessment, control, communication and review of risks to the drug product. It can be applied both proactively and retrospectively. Hence, an effective QRM approach can further ensure the high quality of drug product to the patient by providing a proactive means to identify and manage potential quality issues during development and manufacturing. Effective QRM can facilitate better decisions and beneficially affect the extent and level of direct regulatory oversight.

As disposables components become more widespread in drug product manufacturing, it is important to apply QRM principles to assess the extractables/leachables risks to product quality and patient safety.

There are clear U.S. FDA, EMA and ICH guidelines and regulations for leachables due to the impact on the safety, quality and efficacy of the final drug products. These regulations and guidelines, however, do not describe how to design the test plan, perform analyses and interpret the extractables and leachables data. The relationship between extractables and leachables needs to be fully understood, as well as how leachables react or behave in process conditions.

The survey showed that most data packages currently available for extractables from suppliers are not technically sufficient for components qualification and process evaluation. Inconsistency of the data from vendor to vendor as well as lack of regulatory guidance has pushed end users toward adapting a variety of risk assessment processes, inclusive of testing for extractables. Some companies are using suppliers' extractables data for initial risk assessments, supported by extractables testing for disposable components. Following testing, a cumulative or individual component approach is used for the second risk assessment. Leachables studies are designed based on the risk severities from the second assessment. All these assessments, as well as testing, can take more than 12 months.

Some of those surveyed have proposed a standard "6 Model Solutions/Solvents Extractables Protocol" for suppliers to test their components, and then standardizing the reporting of their results with a standard user requirement (SUR). This would enable end users to use data in a standard way. Others are also working on standardizing a risk assessment model and leachables design and testing.

2. Common Grounds for Designing Leachable Studies: As leachable testing

remains an end user responsibility, there exists a need for a standardized study design, where possible.

The survey described in the previous article revealed differences on the leachable study design in multiple areas, such as:

- Types of leachable studies conducted when additional tests are required (accelerated versus real-time)
- Multiple timepoints in the context of using disposables for storage purposes
- Consideration of lot variability for disposables as part of the leachables assessment
- Extent of elemental impurities assessed as part of leachables studies
- Evaluation of how the leachables data will be utilized in the safety assessment

The needs of the study design also depend on the purposes of the disposables system in the manufacturing process (storage versus in-process use); primary packaging remains out of scope. Another concern involves sample generation for leachables studies, i.e., scale reduction and mimicking of actual manufacturing process conditions with adherence to materials of construction, existing pretreatments, surface area-to-volume ratio representativeness and relevant product storage conditions. These will all be addressed in the best practices document.

3. Need for a Consistent Analytical Method Approach: The survey also showed agreement in the basic four methods used for leachables testing. These are: HS-GC-MS, direct inject GC-MS, HPLC-UV/MS, and ICP-MS or OES with additional methods, including ion chromatography (IC), total organic carbon (TOC), infrared spectroscopy (IR) and nuclear magnetic resonance (NMR). Companies generally also use quantitation tests on a regular basis. Heavy metals are typically part of the analytical methods chosen by the companies, and these include elemental impurities screening. There was variation in whether leachables methods were validated or demonstrated "fit for purpose" with all variations being accepted by the regulatory agencies.

To ensure development of consistent approaches to analytical methods, the best practices document will answer the following:

- Which methods should be used for the various purposes and types of components being evaluated?
- Can a limited set of methods cover most components?
- Although both companies and regulators seek to achieve patient safety as their objective, how much validation is truly necessary to meet the desires and needs from both companies and regulators?
- Do all typical methods (HS-GC-MS, GC-MS, LC-MS, ICP-MS or OES) need to be used to evaluate each component?
- Should all standard methods be used and performed in a screening mode to demonstrate unexpected compounds are observed if present?

Conclusion

Based on BPOG members' experiences, the lack of regulatory requirements supporting disposables components and expectation alignments between reviewers and inspectors are of great concern and frustration. In addition, regulators often request that extractables and leachables data taken at any point during the manufacturing process be used to support the use of disposables in terms of risk. For this reason, BPOG has launched the development of best practices in support of a risk assessment model and flow diagram, leachables study design and analytics. It is hoped this effort will drive best practices within industry and allow end users to efficiently qualify new materials while at the same time maintaining the high level of quality assurance and safety expected for pharmaceutical/biopharmaceutical products.

Acknowledgement: This effort would not be possible without the groundwork and effort of the BPOG Extractables and Leachables Team, which is a larger group of subject matter experts from participating pharmaceutical and biopharmaceutical companies working collaboratively to advance the science of extractables and leachables.

The team of authors behind this article consisted of ***Christopher Smalley, Weibing Ding, Gary Madsen, Kathryn McGohan, Christian Menzel, Dhavel Tapiawala, Ping-Ping Wang*** *and* ***Ken Wong.***

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Why is Patient Convenience Important?

Olivia Henderson, PhD, Amgen

"Patient convenience" is a phrase that has been used for a couple of years now. This concept is still a primary driver in drug development. Why is it so important? After all, the word "convenience" can imply a scenario of enabling jet-setters to obtain their routine medication with ease while flying from one glamorous location to another.

If this were really the case, then companies engaged in drug development would not spend much time on patient convenience. Rather, the move toward patient convenience means factoring in a different set of demographics. These include busy parents of young children, working professionals and elderly patients clinging to independence. Patient convenience has many benefits as well, such as reduced visits to healthcare professionals which results in cost savings for insurance companies. In addition, patient convenience options may improve patient compliance rates, thereby improving patient outcomes.

Failure to factor in patient convenience can lead to negative outcomes. Consider heart attack patients. Research has shown that one in five prescriptions for patients hospitalized for heart attacks remain unfilled after 120 days ***(1).*** This lack of compliance involving an *oral dosage form* yields a grim prognosis for injectable medications.

The first component of patient convenience is the prefilled syringe. The patient can be given the prefilled syringe and directed to self-administer the medication at a specified time, preempting a visit to a doctor's office. Anxiety around needles, however, may inhibit patients from self-administration, leading to the widespread use of pens and autoinjectors, the second component of patient convenience. But pens and autoinjectors are not always discreet; a desire for privacy may lead to missed doses, and consequently, a lack of compliance. This leads to the third component of patient convenience: tracking patient compliance by use of smartphone apps and/or connectivity with the device. By analyzing

Continued at bottom of page 19

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Biosimilars Offer Much to Consider for Biopharma

Michael VanDerWerf, Teva

Revenues for biosimilars are expected to reach $35 billion by 2020, according to Allied Market Research, growing from an estimated $1.3 billion in 2013. This tremendous growth trajectory is being driven by multiple factors: pressure from third-party payers to trim the costs of the many biopharmaceuticals in use today, patients living longer but beset by disorders that require maintenance drugs, increasing analytical innovation that can be used to establish the similarity of complex biologics, and most importantly, the emergence around the word of regulatory pathways for biosimilars/follow-on biologics.

For these and other reasons, biosimilars are now one of the current focus areas of PDA's Biotechnology Advisory Board (BioAB). This group is composed of biotech experts drawn from PDA's membership and serves to identify, discuss and seek resolutions to issues impacting the biotechnology industry.

PDA has been at the forefront of biopharmaceutical development and manufacturing since the first recombinant products reached the market in the 1980s. Now, in the era of engineering copycat biopharmaceuticals, PDA is proud to announce the *2016 PDA Biosimilars Conference*. This meeting is being organized to ensure constructive dialog between industry and regulatory agencies in order to explore interpretations and facilitate solutions. The two co-chairs of the conference—**Vince Anicetti,** Senior Vice President, Quality and Compliance, Coherus Biosciences, and **Stephan Krause,** PhD, Director, QA Technology, AstraZeneca Biologicals—are both members of BioAB.

The two-day event kicks off with the plenary session, "Current Agency Expectations for Approval of Biosimilars." The session will feature multiple speakers from various regulatory bodies providing their experience and views on the key aspects needed for a biosimilar development program as well as the framework for what ought to be included in a marketing application. Regulatory speakers have been invited from the U.S. FDA, Health Canada and Europe. Presentations will offer a mix of both CMC and clinical considerations.

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Since one of the critical elements of a biosimilar application is the CMC section establishing the similarity, the next session—"Establishing a QTPP for Biosimilars"—will be a deep dive into preparing a quality target product profile (QTPP) that recognizes the key quality attributes of the molecule and its mechanism of action. The QTPP then drives the data to be collected in support of the marketing application and supports the lifecycle of the product.

Further sessions will look at demonstrating analytical similarity, postmarketing change management, product specifications, and more.

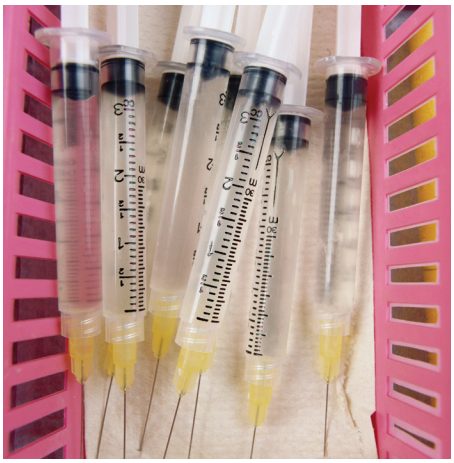
Why is Patient Convenience Important? continued from page 18

this specific data, the physician can then modify treatment options as needed.

The different aspects of patient convenience are in a state of change and innovation. Even the basic building block—the prefilled syringe—is undergoing modifications by many suppliers through the use of new construction materials and enhanced manufacturing processes intended to improve compatibility with the drug product and/or reliability of supply.

Therefore, it is more important than ever to be up-to-date with the latest developments in prefilled syringes, materials, manufacturing, smart devices and connectivity. At the 2016 *Universe of Pre-filled Syringes and Injection Devices,* participants can see presentations and posters on the latest innovations, network with others in the field, meet new colleagues and stay abreast of the latest breakthroughs in patient convenience.

[Editor's Note: For more on patient convenience, see "Pens, Injection Devices Get "Smarter," March *PDA Letter*.**]**



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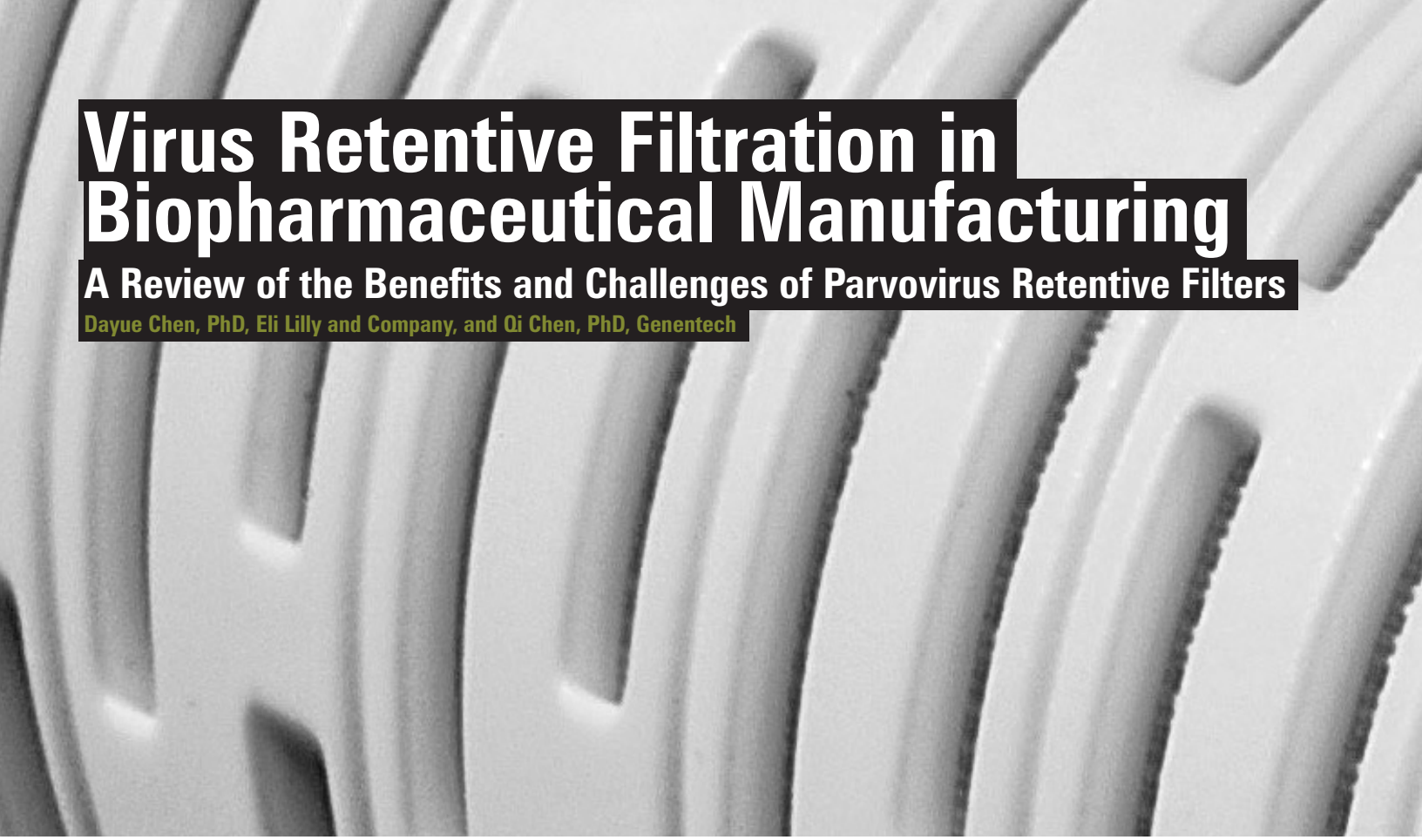

Virus Retentive Filtration in Biopharmaceutical Manufacturing

A Review of the Benefits and Challenges of Parvovirus Retentive Filters

Dayue Chen, PhD, Eli Lilly and Company, and Qi Chen, PhD, Genentech

Virus removal

using retentive filters designed to provide effective and consistent clearance of parvovirus (~20 nm) has now become an established standard in downstream purification processes for biologics produced using mammalian cells ***(1).*** Compared to other commonly used virus clearance methods, such as chromatography and low pH inactivation, retentive filtration is superior in its ability to clear almost all potential viral contaminants while also avoiding adverse effects on product quality. While commercially available retentive filters vary in chemical composition and structural configuration, all of these filters primarily clear viruses through the mechanism of size exclusion ***(1–3).***

Consequently, it is no surprise that parvovirus filters can consistently provide reliable and effective removal of larger viruses, such as ~100 nm retroviruses ***(1,4–5).*** It is now increasingly common for firms to claim retrovirus clearance based on either previous in-house experience or studies carried out with parvoviruses to support clinical trial applications ***(4–5).*** Regulators worldwide are generally receptive of such an approach.

There are two different schemes to claim modular retrovirus clearance in place of performing molecule-specific laboratory scale retentive filtration studies.

The first approach entails using existing in-house retrovirus clearance data to justify a specific log reduction factor (LRF) as the modular retrovirus clearance capacity for the retentive filtration unit operation for any future processes ***(4).*** This approach is justified by the fact that no retrovirus breakthrough has ever been observed or reported when a cell-based assay is used for virus titration ***(1).*** The advantage of this approach is that, once established, it has a constant modular LRF applicable to future processes, making it easy to estimate how many additional LRFs are needed in order to meet the regulatory expectation for retrovirus clearance and plan accordingly. A significant amount of preexisting in-house retrovirus clearance data, however, is required.

The second approach considers parvovirus as the worst case model virus because of its much smaller size than retroviruses, or any other commonly used model viruses. This approach also uses the parvovirus LRF to represent the universal clearance capacity of the unit operation for all model viruses ***(5).*** The advantage of this approach is that it does not require any existing in-house retrovirus clearance data for the given retentive filter. Yet, any potential parvovirus breakthrough could impact the claimable retrovirus clearance LRF. When used in full accordance with regulatory expectations ***(6–7),*** the modular retrovirus clearance approach allows firms to reduce the number of viral clearance studies needed to support clinical trial applications and ensure the viral safety of product.

Be Wary of Parvovirus Breakthrough

Parvovirus retentive filters have improved significantly in recent years with regard to performance consistency, volumetric throughput and process time. The second generation parvovirus filters such as Viresolve® Pro (EMD Millipore),

Significant efforts are needed in order to better understand the mechanism of parvovirus breakthrough

Virosart® HF (Sartorius), and Planova™ BioEx (Asahi Kasei) are all less prone to parvovirus breakthrough. Still, parvovirus breakthrough continues to be a concern for regulators, biopharmaceutical companies and filter manufacturers since the breakthrough mechanism and critical process parameters (CPP) that influence the filter performance remain not completely understood ***(3).***

Filtration flux decay has been linked to virus breakthrough for certain brands of first generation retentive filters. Some hypothesize that small pores in the filters are progressively plugged by viruses and protein aggregates, resulting in flux decay over time, eventually forcing viruses to pass through filters via available larger pores ***(8–9).*** It has also been observed that process interruptions (pressure release) during retentive filtration could potentially cause parvovirus breakthrough ***(10–11).*** The exact underlying mechanism for the phenomenon is not entirely clear. It has been reported that significant parvovirus breakthrough requires the process interruption to persist for at least three minutes or longer. Furthermore, low flow transmembrane pressure promotes parvovirus breakthrough, suggesting that diffusion may play a role in the observed breakthrough ***(11).***

A study using bacteriophages labeled with two fluorescence dyes and confocal microscopy has shown that bacteriophage retention patterns varied among the three different filters examined following a 10-minute pause in flow ***(12).*** These results are consistent with the fact that not all retentive filter brands are susceptible to process interruption ***(11).*** The correlation between process interruption and parvovirus breakthrough in some filter brands has drawn significant scrutiny from regulators during marketing application review and preapproval inspection processes. Therefore, for these types of filters, it is essential that parvovirus clearance studies evaluate these parameters and carefully assess the potential risk. Effective measures/controls in manufacturing should be implemented based on the virus clearance study results.

Retentive filtration is a dedicated virus clearance unit operation; achieving reliable and robust virus clearance is obviously its most important goal. Retentive filters, however, represent one of the most costly consumables in biopharmaceutical manufacturing. Therefore, it is logical to target the maximum volumetric throughput (l/m^2) during process development, as this could potentially save millions of dollars over the lifetime of a given product. When process time is predetermined and fixed, the volumetric throughput (l/m^2) is a function of the filter flux (l/m^2/h), which may be influenced by many different factors, such as

Article at a Glance

- Retentive filters now a standard for viral clearance
- Parvovirus breakthrough still a concern to industry, regulators
- Filtration using retentive filters is costly, making robust virus clearance key

the inherent permeability of the membrane, transmembrane pressure, pH, conductivity, impurity levels, aggregates, product concentration, viscosity and, finally, the virus spikes. All of these factors, with the exception of virus spikes, are determined either by the purification process, biochemical/biophysical properties of the molecule, or both.

Filter performance measured by flux (l/m^2/h) and/or virus clearance can be substantially impacted by the quality as well as the quantity of virus spikes ***(13–15).*** A recent survey has revealed that quality attributes of virus spikes used in virus clearance studies vary greatly ***(16).*** It is critical, therefore, to use highly purified virus preparations in virus clearance studies to minimize the adverse impact on the filter flux. While there is currently no established quality standard or criteria for virus preparations, the quality attributes defined in *PDA Technical Report No. 47: Preparation of Virus Spikes Used for Virus Clearance Studies* should be considered when selecting or preparing virus spikes for filtration studies.

In summary, implementation of parvovirus filters in the downstream process has become an industry standard and regulatory expectation in recent years. These filters have consistently demonstrated highly effective retrovirus retention and absence of impact to product quality across a wide process parameter ranges. Parvovirus filters made by different manufacturers differ in their chemistry and structural configuration, leading to different operating pressures, flux rate and susceptibility to certain process conditions. Significant efforts are needed in order to better understand the mechanism of parvovirus breakthrough and CPPs involved. It might be unrealistic, however, to expect that CPP, or mechanisms identified from a given study with a particular brand filter will be applicable or relevant to other filters. Nevertheless, parvovirus retentive filters have provided an effective, orthogonal method to significantly reduce adventitious virus risks in biopharmaceutical manufacturing.

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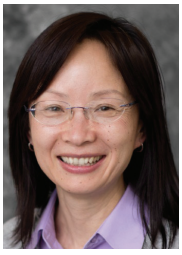

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Missed Opportunities for Adventitious Agents Testing

Sven M. Deutschmann, PhD, Roche Diagnostics GmbH

Current adventitious agent test methods feature numerous limitations. Assays based on polymerase chain reaction (PCR) offer the potential to lift these limitations and offer better overall detection of adventitious agents. This is an area that biologics manufacturers are actively exploring, and current research indicates that PCR-based testing is not only scientifically valid but also acceptable to regulators (see sidebar, next page).

The Present State of Testing

The use of testing methods to detect adventitious agents in biologics manufacturing is a requirement by global regulators. During the manufacturing process for biologics, manufacturers utilize eukaryotic expression systems which can be prone to microbial contaminations. This means that these processes require strict microbial control strategies, including testing for adventitious agents that generally consist of mycoplasma, *Leptospira* and viruses.

At this time, detection methods for traditional adventitious agents require the following:

- Significant manual handling of the specimens
- Up to 28 days for results (in the meantime, mycoplasma, Leptospira or viruses could contaminate the expensive downstream processing equipment, resulting in a possible supply disruption)
- Well-trained analysts with a high level of expertise for interpreting results
- Specialized equipment and laboratories

Additionally, detection methods for traditional adventitious agents used at present carry a number of limitations. These can result in missed opportunities as presented in **Table 1.**

In recent years, increasing concerns have been raised regarding the sensitivity and/or specificity of traditional detection assays for adventitious agents.

Table 1 Traditional Adventitious Agents Detection Methods: Current Limitations and Missed Opportunities

Issue/Pain	Missed Opportunities
• Some cytotoxic New Molecular Entities (NMEs) interfere with in vitro cell culture assays • Low sensitivity (due to dilution needs – see bullet above) • Limited specificity • Different assay platforms • High effort due to manual handling • Complex sample workflow • Specialized equipment and dedicated laboratories • Lengthy testing times • Results interpretation requires high level of expertise • Safety, health and environment issues	• Non-"state-of-the-art" assays • One common platform • Simplification • Agility, flexibility • Cost savings • Sample processing automation • High throughput testing • Early detection of contaminations

Table 2 Sensitivity of Rodent Parvovirus Detection Assays

Rodent Parvovirus / [Species and Strain]	Sensitivity of the 324K-cell-based assay / [$TCID_{50}$/mL]	Sensitivity of the PCR-based assay / [$TCID_{50}$/mL]
Kilham's rat virus (KRV)	> 10	0.003
Mouse Minute Virus (MMV17)	> 10	0.14
Mouse Minute Virus (MMV52)	> 10	0.27
H1-Parvovirus	0.86	0.02

Sensitivity: Validation studies demonstrate the superiority of PCR-based rodent parvovirus detection assays over the traditional 324K cell-based detection assay (see **Table 2** for the summary of validation results).

Lack of specificity: A biopharmaceutical company discovered that mouse minute virus (MMV) had contaminated its Chinese hamster ovary (CHO) cell production system ***(1).*** Neither the in vitro general viral screen nor the 324K cell assays detected this MMV strain; however, the MMV strain can be reliably detected using a PCR assay. This clearly shows that not all viruses can be detected by cell-based in vitro viral screen assays. In addition, this limited specificity that translates into potential inaccuracies in detecting contaminants has been confirmed not only for viral contaminants but also for bacterial contaminants. For example, *Spiroplasma citri* cannot be detected by the traditional growth- and cell-based mycoplasma-detection assays ***(2).***

While this limited specificity is a current challenge for the development of NMEs, it will be an even greater challenge in the future. Some of the NMEs, such as anticancer therapeutics, interfere with traditional in vitro cell culture-based detection methods for adventitious agents. The mode-of-action of some NMEs is based on cellular cytotoxicity. Cytotoxicity-induced cell death not only kills the oncogenic target cells but also the permanent cell lines used as indicator cells for the traditional

in vitro detection methods. Therefore, the testing sample needs to be diluted (product-dependent up to 1:10.000), resulting in very low sensitivity of the traditional in vitro detection methods. It is questionable if this situation will be tolerated by regulators in the future. Guidance documents have already been published by regulators recommending PCR-based methods ***(3)*** for specific target organisms.

Another example demonstrating the acceptance of PCR-based detection methods by regulators can be found in the U.S. FDA's Level 2 guidance *Q&A on Current Good Manufacturing Practices—Production and Process Controls* ***(4).*** Question 14 asks whether biologics manufacturers' microbial control strategies are capable of detecting unusual microbiota such as *Leptospira* and recommends the "use of validated PCR methods (e.g., as an investigative tool) for rapid screening and detection of spirochete bacteria."

To address the potential limitations of the traditional detection methods (see **Table 1**), several companies have introduced multiyear programs, with new, fully automated PCR-based methods using automated equipment for the purification of the target nucleic acid and real-time PCR amplification and detection systems.

Automated PCR-based testing methods for adventitious agents detect contaminants within five to eight hours. This allows biopharmaceutical companies to isolate the contamination to upstream and harvest equipment without contaminating expensive downstream equipment. No additional and subsequent processed lots using the contaminated downstream equipment are contaminated secondarily. Decontamination efforts are then less extensive, resulting in reduced facility shut-down times. In general, PCR-based adventitious agents detection methods significantly reduce reaction times, minimize the impact of

Regulatory Guidelines in Support of PCR-based Testing

ICH Topic Q5A, "Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin", CPMP/ICH/295/95, 1997

ICH Topic Q5D "Derivation and characterisation of cell substrates used for the production of biotechnological/biological products", CPMP/ICH/294/95, 1998

FDA, Guidance for Industry Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications, February 2010

EDQM, Ph. Eur. Monograph "Viral Safety" (50107)

EDQM, Ph. Eur. Monograph "Monoclonal antibodies for human use" (2031)

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EDQM, Ph. Eur. Monograph "Mycoplasmas" (20607)

any potential contamination on the product supply, and ensure uninterrupted supply to patients.

Additional benefits are higher throughput and higher reliability, as the PCR-based methods have the capability to be executed on fully automated robotic platforms without the need for manual intervention, thus avoiding safety, health and environmental hazards, including ergonomic issues such as repetitive strain injury. Other benefits include cost savings, improved productivity, and increased agility and flexibility in the testing network.

Global Regulators Accept PCR

Companies are achieving considerable benefits by moving to PCR-based assays for adventitious agents. A decade ago Roche began using PCR-based adventitious agents tests, and this author presented them at the *2016 PDA Annual Meeting* ***(5).***

The company achieved a significant milestone in 2013 during the first phase of the program: FDA approval of the first generation PCR-based mycoplasma detection method as a replacement for traditional mycoplasma detection methods ***(6)***. This marked the last of global approvals necessary for this new PCR-based analytical technology.

Roche obtained the first approval for this method in 2009 in Europe, then in Japan in 2010, followed by approvals in more than 120 countries—indicating that global regulators are increasingly accepting PCR-based mycoplasma detection methods.

In 2014, Roche achieved the milestone of the second phase of the program: FDA approved the Leptospira-PCR that used a fully automated technology platform, as part of a biologics filing (additional approvals were obtained in the meantime by other regulatory bodies worldwide), demonstrating further acceptance by regulators for modern, fully automated, real-time PCR-based adventitious agents testing.

In the meantime, this second generation PCR assay platform is used not only for the PCR-based detection of *Leptospira,* but also for the detection of mycoplasma, and rodent parvoviruses. All assays use the same fully automated nucleic acid purification equipment and real-time amplification and detection equipment platform. Beyond the commercial product portfolio, Roche plans to use these new assays for biologic Investigational Medicinal Products in 2016.

Roche's experience moving to PCR-based adventitious agent testing shows that regulators across the globe recognize the limitations of traditional tests. As industry moves forward, adoption of PCR and other more advanced adventitious agent tests will only increase. Biologics manufacturing is a growing field and it only makes sense to use improved assays in this area.

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About the Author

Sven Deutschmann joined Roche Diagnostics GmbH as Manager of QC in 1995. Since 2001, he has been director of the QC department.

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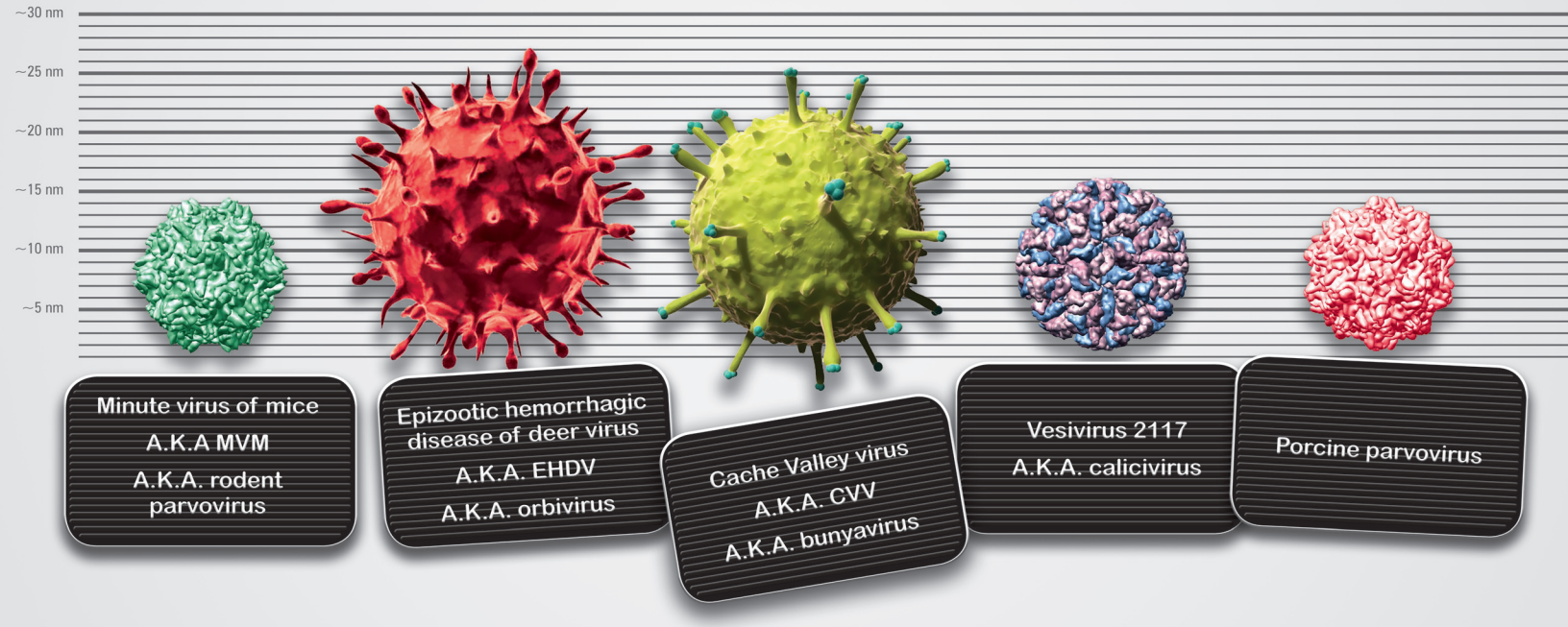
THE "USUAL SUSPECTS" OF VIRAL CONTAMINATION

Biopharmaceutical manufacturing utilizes cell lines from living organisms. These cell lines can be contaminated with viruses. Below are some examples of viruses that have contaminated cell lines in biologics manufacturing.



- Common among wild mice
- Can contaminate cell lines such as Chinese hamster ovary cells
- High-temperature, short-time (HTST) mammalian cell media treatment may offer protection

- Although primarily found in deer, cows located in areas where the disease is prevalent can be infected
- Found in bovine serum, contamination occurs during biologics manufacturing processes employing Chinese hamster ovary cell substrates
- Gamma irradiation of frozen serum could be used to prevent it

- Primarily found in cattle and sheep
- Found in bovine serum, contamination occurs during biologics manufacturing processes employing Chinese hamster ovary cell substrates
- Gamma irradiation of frozen serum could be used to prevent it

- Affects mammals
- Interferes with the growth of Chinese hamster ovary cells
- Can be introduced through fetal bovine serum

- Causes reproductive failure in swine
- Associated with contamination of the raw material trypsin
- Gamma irradiation could be used to prevent it

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snapshot

Survey on Pharmacopoeial Use Offers Wealth of Info

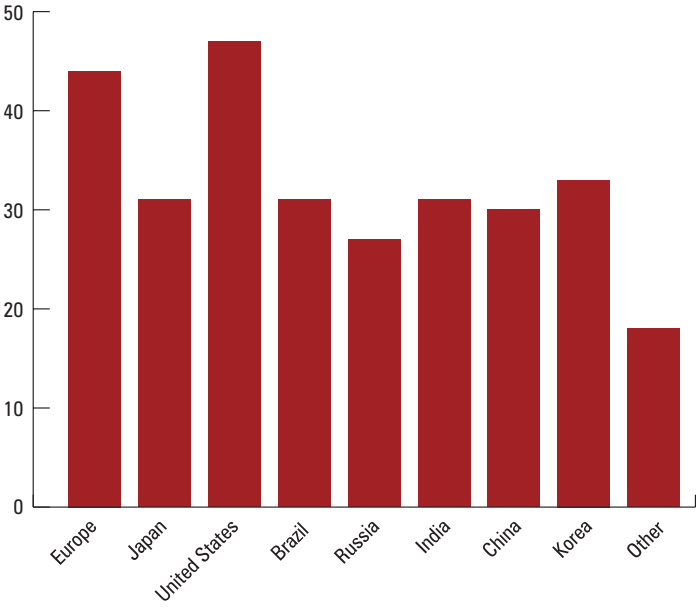
Karen Ginsbury, PCI

In 2015, PDA's Pharmacopoeial Interest Group conducted a survey via PDA Connect℠ on pharmacopoeial use. Members from 64 countries, representing a range of different companies from CMOs to generics firms, responded. The survey will be published later this year and available for purchase from the PDA Bookstore (www.pda.org/bookstore).

Below are some highlights from the survey that drew the attention of the leaders of the Pharmacopoeial Interest Group.

Of the survey respondents, 67% manufactured finished dosage forms and 40% produced API, with approximately equal distribution between small and large molecules. When it comes to the various global pharmacopoeias, 98% of respondents put the U.S. Pharmacopeia (USP) at the top of the list. The European Pharmacopoeia (EP) came in second at 83%, and the Japanese Pharmacopoeia third at 55%. WHO's International Pharmacopoeia received the least amount of use at just 19%. The reliance on the USP and EP may reflect the nature of PDA's membership, which skews heavily toward the United States and Europe. Yet respondents' product licensing is spread around the world, almost in equal segments (**Figure 1**).

Figure 1 In which territories is your company licensed to market product?



Another interesting finding concerned Full Time Equivalents (FTEs) assigned to monitor pharmacopoeial updates. 50% of respondents have between 1–5 FTEs and 14% have *more than ten*. While this was only a preliminary survey, it is clear that staying up-to-date on pharmacopoeial issues requires a concerted effort on the part of a company in addition to dedicated resources.

Along these same lines, the survey included the question, "Does your company provide a formal training/qualification course or program for proficiency in using and monitoring pharmacopoeias?" 76% answered "no." This response was qualified in several cases with some explanations as to how they still ensure proficiency. But it is clear, despite the complexity and number of pharmacopoeias and their updating mechanisms, that the vast majority of companies do not offer formal courses/programs on the various pharmacopoeias or test proficiency of pharmacopoeia use. The interest group leaders believe it would be worthwhile to reach out to those companies with five or more FTEs to see if there is a harmonized approach to their monitoring of the various pharmacopoeias within their companies.

Respondents also offered some general comments. Several pointed to the need for pharmacopoeial harmonization—a topic the interest group has begun discussing. Others want easier access to changes similar to the European Pharmacopoeia Knowledge database. Another suggestion involved developing a table to illustrate the equivalences between titles of methods and monographs, especially between the USP and EP. Questions from respondents included: "How do you assure each employee receives timely notifications of revisions or updates?" and "What electronic systems are commonly utilized for tracking compendial updates?"—the latter of particular importance for global firms.

For an initial survey, it has certainly provided a lot of food for thought. Those interested in this survey of pharmacopoeial use are encouraged to follow continuing developments in the Pharmacopoeial Interest Group discussion on PDA Connect℠ (community.pda.org) and by attending the interest group's upcoming meeting in September at the *2016 PDA/FDA Joint Regulatory Conference* in Washington, D.C.

About the Author

Karen Ginsbury is President and CEO of PCI, Pharmaceutical Consulting Israel Ltd., a company which provides services to the pharmaceutical, biotech and allied industries. With many years of hands-on industrial experience, she has designed, implemented and maintained company-wide compliance systems, which have passed Israeli Ministry of Health, U.S. FDA and European inspections for both small start-ups and large pharma.

When do ATMPs Fall Under GMP in the European Union?

Ursula Busse, PhD, Novartis

[Editor's Note: The following is a response to the article, "Divergent Approaches to Stem Cell Regulation" published in the January *PDA Letter.* Here, **Ursula Busse** responds with a European perspective on regenerative medicines regulations**.]**

Over the past decade, European legislation has laid out specific GMP requirements for products referred to as "advanced therapy medicinal products" (ATMPs) or "regenerative medicines."

ATMPs are now defined as one of three categories: a gene therapy, a somatic cell therapy or a tissue-engineered medicinal product. The latter is defined as a medicinal product that contains cells or tissues that have either been "substantially manipulated" or will not be used in their original function ***(1).***

According to the EU's ATMP Regulation ***(1),*** cells or tissues shall be considered "engineered" if they fulfill at least one of the following two conditions:

- The cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions, or structural properties relevant for the intended regeneration, repair or replacement are achieved. Procedures during manufacturing like cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation and vitrification are not considered to be substantially manipulated.
- The cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

GMP production requirements apply to all therapeutics that go beyond the usual "minimal manipulation" steps required for the isolation and preparation of, for example, hematopoietic stem cells, bone marrow and lymphocytes.

These products will have to undergo a marketing authorization procedure, unless they are exempted in accordance with Article 28(2)4 of Regulation (EC) 1394/2007. This exemption, referred to as the "hospital exemption" applies to ATMPs prepared on a nonroutine basis according to specific standards, and used within the same member state in ➤

a hospital while under the exclusive professional responsibility of a medical practitioner. Such products must also be custom-made for an individual patient as part of a prescription.

Last July, the European Commission issued the long-anticipated draft guideline, *Good Manufacturing Practice for Advanced Therapy Medicinal Products* ***(2).*** This guideline covers GMP requirements for both investigational and commercial ATMPs. Comments were collected from industry. A summary of these comments was published in December ***(3).***

The majority of industry respondents supported the approach described in the draft guideline. In particular, academia and small/medium sized companies deemed the proposed adaptations of GMP requirements useful and beneficial. The application of risk-based approaches, as well as adapted requirements for raw materials, was widely supported. Respondents felt that more flexibility was needed with regard to manufacturing environments, e.g., when isolators or semiclosed systems are used. And many suggestions were made on how to adapt GMPs to ATMP manufacturing using automated devices/systems. Once finalized, the guideline might well influence the future of innovative pharmaceutical technologies in the European Union.

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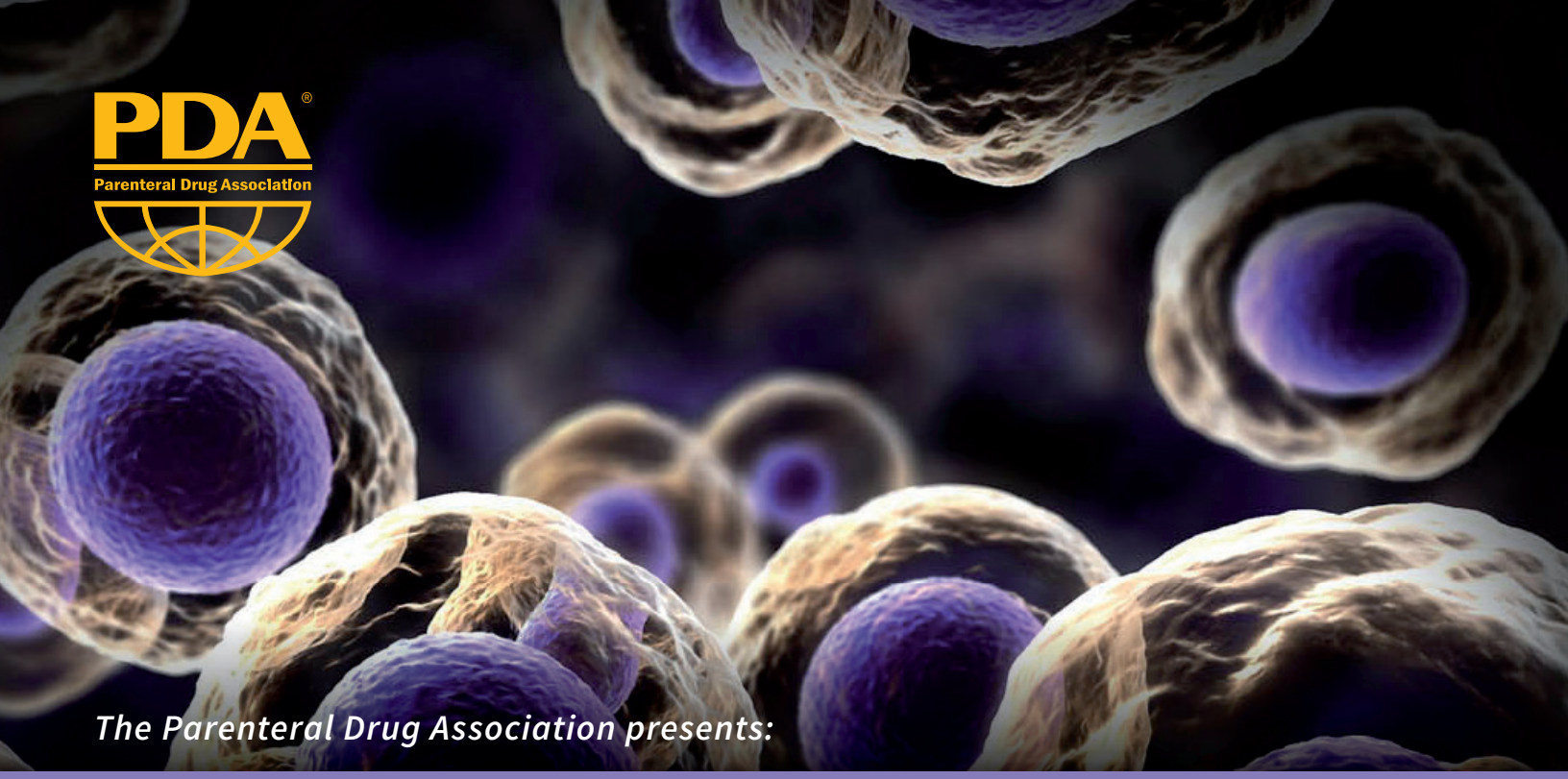
About the Author

Ursula Busse, PhD, currently holds a global position as Head of Quality Intelligence for Group Quality External Relations at Novartis.



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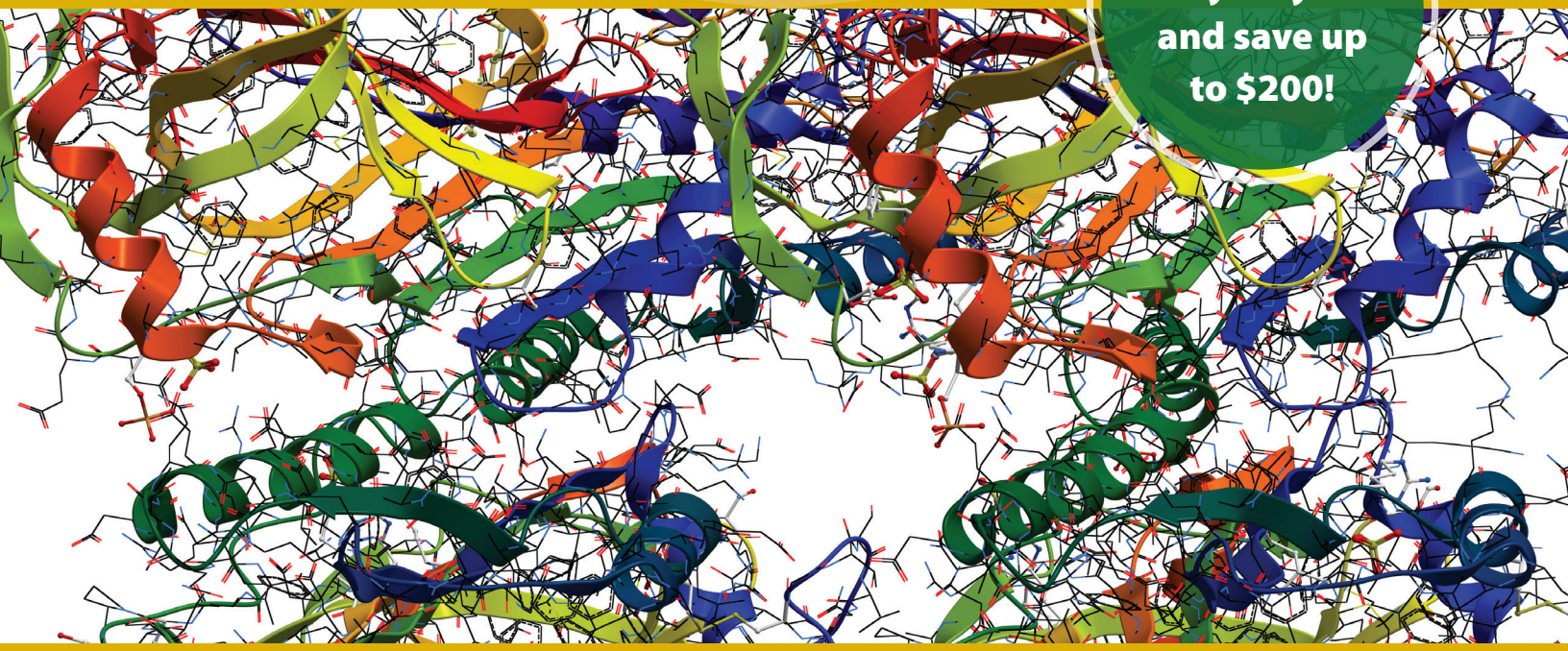

In order to meet industry's need for information on this increasingly important topic, PDA is introducing a new event, the *2016 PDA Biosimilars Conference*.

Throughout the Conference, successful case studies and practical examples will be used to illustrate how analytical similarity can be demonstrated and practical control strategies can be developed. Current updates from regulatory agencies, including the U.S. FDA, EMA and Health Canada, will be presented, and CMC reviewer perspectives will elucidate those CMC issues that have been most challenging to approve. Attendees will have the opportunity to raise questions and concerns during the conference.

For more information and to register today, please visit pda.org/2016Bio.

Immediately following the Conference, two courses will be held on biosimilar CMC and regulatory challenges and analytical method qualification, transfer and validation for biosimilars.

For more information on these courses and to register today, please visit pda.org/2016Biocourses.

#2016Bio

New USP Chapters Offer Visual Inspection Harmonization Hope

Roy T. Cherris, Bridge Associates International LLC

If you are responsible for visual inspection programs, you most likely have been wrestling with what exactly it means for a product to be "essentially free" or "practically free" from visible foreign particles. This language has been the standard—with variable meaning—until August 2014 when USP <790> *Visible Particulates in Injections* became official. Then, last year, USP released draft general guidance chapter <1790> *Visual Inspection of Injections.*

It is clear that with the issuance of these chapters, along with other recent publications, we now have an opportunity to harmonize our industry's approach to the fundamentals of inspection. Harmonization of inspection and defect control in our industry will not happen overnight; it will require both short- and long-term action plans in each organization to achieve this goal.

With this in mind, the *2016 PDA Visual Inspection Interest Group Workshop* will offer an open forum for discussion and clarification of specific topics, such as manual visual inspection best practices and how to approach supplemental destructive testing of products that are difficult to inspect 100% for particulates. Acceptable Quality Level (AQL) inspection will inevitability be covered as well. Morning sessions will cover <790> and feature USP speakers.

Automated inspection is the next logical step as production volume dictates a move from manual inspection. The afternoon session of this workshop will focus on best practices and challenges associated with the implementation and qualification of automated inspection equipment.

The organizers of this workshop hope that attendees leave with a better understanding of visual inspection, resulting in further harmonization of approaches to inspection and control of visible particulates.

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PDA and FDA: A Long History of Collaboration

David J. Cummings and Richard L. Friedman, U.S. FDA

For 25 years, PDA and the U.S. FDA have collaborated on the common goals of improving the quality of medical products for the American public and providing educational opportunities for the medical products industries. The common commitment of industry, academia and regulators to deliver high quality products to patients around the globe serves as the foundation for this collaboration.

Since the first *PDA/FDA Joint Regulatory Conference* held in 1990, PDA and FDA have joined forces to enhance the various medical products sectors' understanding of the implications, expectations and requirements of new regulatory initiatives and to convey current FDA thinking. While there has been monumental regulatory transformation over the years, this meeting has been a constant in successfully and consistently translating the ever-expanding and evolving public and private sector framework into a lexicon of terms and modern strategies aimed at advancing collective understanding. In addition, this meeting has encouraged efforts toward regulatory harmonization, regulatory science policy, cGMPs, contributing factors leading to drug shortages and the effects of industry globalization. These topics have been selected by meeting organizers to assure that consistently safe and effective drugs are available to consumers throughout the entire commercial drug lifecycle.

The expansiveness of the topics addressed at the *PDA/FDA Joint Regulatory Conference* is reflective of the many complexities faced by medical product stakeholders. For example, more than 80% of drugs dispensed today are generics, with approximately 75% of drug manufacturing sites located outside the United States. This creates a particular range of risks for patients, such as increased counterfeiting, false data, tampering and diversion. Preventing these risks has become more complicated in recent years due to a complex supply chain that includes brokers, traders, distributors and repackagers along with import and export firms.

All of these issues require adequate understanding as well as industrial and regulatory strategies that ensure the quality and safety of medical products, including:

- Communicating advances in medical products and technology in the various medical product sectors
- Emphasizing the changing demographics of U.S. patients, the customer base for the medical products industry, while sharing their experience with these life-giving products
- Keeping the medical products industry aware of progress on the Pharmaceutical cGMPs for the 21st Century initiative
- Offering case studies to facilitate learning on new programs, such as the application of Process Analytical Technology (PAT) and monitoring manufacturing process bioburden
- Introducing the concepts and principles that frame Quality by Design (QbD)
- Providing a forum for dialogue on domestic and international standards development and regulatory review partners
- Collaborating with the medical products industry on the application and understanding of risk management principles
- Addressing the challenges of regulatory oversight for products that span multiple regulatory entities such as combination products
- Identifying opportunities to improve the expanding use of CMOs
- Educating the medical products sectors on evolving ICH guidelines
- Presenting the concept and principles associated with lifecycle management manufacturers of medical products
- Highlighting FDA and medical product initiatives to ensure drug safety oversight
- Shepherding the evolution of quality management system principles and implementation efforts within FDA and among medical product sectors
- Cultivating the manufacturing industry to pursue sustainability requirements, and support the application of sustainability for the industry

FDA looks forward to celebrating the 25th year of this important conference with PDA. This year, the meeting will focus on product quality, science, innovation and lifecycle management, in addition to exploring current challenges and opportunities. More specifically, attendees will hear from FDA Center leaders on specific medical product initiatives. Attendees will also learn about risk-based audits, cybersecurity issues, comparability of biosimilars, among others, and the dialogue will continue on topics such as quality system evolution, global supply chain management, and clinically relevant specifications.

The conference is designed to provide a number of great opportunities to engage with FDA and industry colleagues on how we can collectively advance our industry and promote public health for millions of American and international patients.

Please join us for the *2016 PDA/FDA Joint Regulatory Conference* this September.

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Quality Metrics: An Ongoing Journey

Dipti Gulati, PhD, PJI Biotech

Is the journey to a quality metrics-based inspection approach as envisioned by the U.S. Food and Drug Administration Safety and Innovation Act (FDASIA) coming to an end?

The U.S. FDA's quality metrics initiative (QMI) will require each production facility to provide data about the "Quality Level" of the facility. From this data, FDA will then monitor how well the company maintains the quality system and also assess the facility's quality or compliance risk. This collected data will not only support risk-based inspections, but also prevent drug shortages by allowing more time for FDA to assist manufacturers in preventing situations that could lead to drug shortages.

QMI Origins in FDASIA Title VII

The quality metrics journey began in 2012 with the passage of FDASIA. Title VII of the legislation increases FDA's ability to collect and analyze data to enable risk-based decisionmaking and advance risk-based approaches as part of the broader shift toward more strategic inspections. In particular, Section 704 of Title VII requires FDA to maintain accurate electronic registration using a "unique facility identifier." Section 705 requires the Agency to replace frequent biennial inspections with a risk-based inspection schedule for domestic and foreign manufacturers. Section 706 gives the FDA authority to obtain certain records from a drug manufacturer in lieu of, or in advance of, an inspection.

In response to these requirements, FDA indicated the Agency's intention to collect a standard set of quality metrics from life science companies to support the risk-based inspection approach. FDA has even initiated a comprehensive new organizational structure and framework of its inspection activities as part of an effort to address this shift to risk-based thinking.

Following passage of FDASIA, FDA regularly interfaced with industry stakeholders on the topic of metrics at numerous meetings. **[Editor's Note:** PDA held three workshops on quality metrics in cooperation with FDA.**]** Additionally, the Agency's working group on metrics solicited and reviewed white papers from manufacturers on the data they currently collect and the metrics they consider most valuable.

After almost three years of discussion, FDA issued its long-awaited draft guidance on quality metrics in July 2015 ***(1).*** This document identified the following required metrics: Lot Acceptance Rate, Product Quality Complaint Rate, Invalidated Out-of-Specification (OOS) rate and Annual Product Review (APR) or Product Quality Review (PQR) on time rate. The draft guidance also explains the ten different kinds of data FDA expects manufacturers to submit; this data will be used to calculate quality metrics. In addition, FDA identified optional metrics which could provide further details about quality culture and process capability/performance. The proposed optional metrics are senior management engagement in APR review, CAPA effectiveness related to personnel training and process capability/performance.

The FDA will use the quality metrics outlined in this draft guidance to determine a company's ability to produce high quality product consistently. Manufacturing firms will have a one-year period to learn and report these metrics. If companies do not report these metrics, they could face regulatory actions, such as import alerts.

After FDA issued the guidance, several manufacturers and numerous trade groups, including PDA, submitted their comments to FDA, requesting clarifications and expressing concerns on several key points, such as definitions of reporting establishments, phased implementation approach, reporting based on site versus product, reporting responsibilities of contract manufacturing organizations (CMOs), frequency of reporting, method of submission, impact on excipient manufacturers, etc. ***(2–3).***

Looking to the Future of Quality Metrics

As a result of this discussion, CDER's Office of Pharmaceutical Quality (OPQ) plans to issue a technical document defining relevant terms and providing specifications for submitting metrics data to the Agency. FDA believes that these quality metrics, in conjunction with other data available in the FDA database, will provide important information about the operational reliability and overall effectiveness of a company's pharmaceutical quality system and quality culture.

Alex Viehmann, Operations Research Analyst, OPQ/CDER, presented FDA's short- and long-term vision for its quality metrics program at the *PDA/FDA Joint Regulatory Conference* last September ***(4)***. FDA's short-term plan is three-pronged:

- Investigate and segment the inventory into subpopulations, such as manufacturing type, dosage form, etc.

- Study the collected metrics' potential relationship with FDA's internal quality outcomes, such as inspection results, FARs, recalls, shortages etc.

- Estimate the predictive power of each metric for each subpopulation

FDA's long-term vision is to develop signal detection program using SPC, etc., and potentially predict quality outcomes with the use of quality metrics and other variables. FDA intends to use the quality metrics program as a surveillance tool to enhance early technical "quality" engagement with stakeholders to avoid

drug shortages and enforcement actions. The program is not intended to be enforcement-focused.

Russell Wesdyk, Acting Director, Office of Surveillance, OPQ/CDER, presented a "phased approach" of submission requirements for quality metrics at the *PDA Pharmaceutical Quality Metrics Conference* in November 2015 ***(5).*** He specified that it will take about a year for both FDA and industry to learn how to interpret the data following initial submission of quality metrics data.

Both Russell and **Tara Gooen Bizjak,** Senior Science Policy Advisor, Office of Policy, OPQ/CDER, further emphasized at the quality metrics conference that the intent of the program is surveillance not enforcement. Quality metrics data will be just one of the factor FDA uses to asses a facility and drug product ***(2, 6).*** Russell also stated that the metrics program, along with additional information, will help FDA identify a "Dean's List" of quality operations. Those on this "Dean's List" will undergo fewer inspections and receive less oversight of post-approval changes. The intent of the program is to encourage manufacturers to continuously improve using new technology, Six Sigma projects, etc., and reward high quality firms with less frequent inspections.

To help with implementation of the quality metrics initiative, FDA is building an IT system that will accept and analyze data from manufacturing sites across the globe, explained **Karthik Iyer,** Acting Branch Chief, Office of Quality Business Informatics, OPQ/CDER ***(6).***

Multiple Benefits for Industry

Quality metrics will support several FDA initiatives, such as management of risk-based inspections, prevention of drug shortages and outreach to assist manufacturers in preventing situations that result from quality issues (e.g., recalls, 483s, Warning Letters, Untitled Letters, Consent Decrees, import bans, etc.).

Ultimately, the quality metrics program will not only help FDA implement these initiatives but will also benefit companies by helping them move toward a performance-based culture. The collaborative effort between FDA and industry to resolve quality-related issues will help prevent scenarios that undermine quality operations, thereby reducing the cost of quality.

Manufacturers invest large amounts of resources in hosting regulatory inspectors every year. As a result of this initiative, FDA can conduct fewer risk-based inspections, instead of inspecting thousands of facilities around the world ***(6).*** Lessening the number and frequency of inspections will not only reduce the cost of inspections for FDA, but will also reduce the cost of compliance for manufacturers.

Quality metrics will be calculated differently in different companies—even within the same company. FDA's quality metrics program will standardize the life science industry's approach to monitoring quality systems/processes and driving continuous improvement.

After almost three years of discussion and collaboration with several associations, FDA has identified a list of metrics and issued a draft guidance to define quality metrics. It will be about a year of learning on the part of FDA as well as industry before metrics can be effectively utilized to support the risk-based inspection model. Still, it will take a couple years of learning for all the stakeholders involved before the benefits of the quality metrics initiative become evident.

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About the Author

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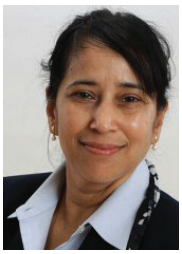

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PDA Supporting Biotech Manufacturing Innovation

The next five years should prove to be a very exciting time for pharmaceuticals, and in particular, the biotech industry. This industry faces the major challenge of providing unprecedented quantities of drug product in an ever-expanding market. Immune-oncology products and monoclonal antibodies are two examples of especially hot biotech products at the moment. Concurrently, biosimilars and advanced therapy medicinal products (ATMPs) are becoming key segments of the overall industry. Compelling issues like these facilitated the creation of PDA's Biotechnology Advisory Board (BioAB). This advisory board provides oversight for PDA's biopharma-focused scientific and technical activities and establishes PDA's strategic direction in this area.

Innovations within pharma manufacturing as a whole are currently focused on continuous manufacturing, single-use systems, automation and robotics as well as the use and integration of electronic data hardware and software to control and document processes. Implementing the analytics necessary to understand and continuously improve processes will be key to achieving success with these innovations. It will be critical for PDA to work with regulators and industry to ensure scientific and quality approaches that will allow these disruptive innovations to come to fruition.

In response to these developments within traditional pharma, the BioAB is currently focusing on technologies that revolutionize how biotech products are manufactured in the face of the coming demand. Over the last 20 years, the objective has been increasing titers, with many facilities now hitting 10g/L, 1000 times the titers of the past, as well as improved downstream processes, resulting in increasing yields. While these innovations have moved the industry forward, it seems that now may be the time to revolutionize how both manufacturers and regulators think about biotech manufacturing in order to address the perceived need for vastly increased throughput. As part of this effort, PDA will offer the course, "Implementing Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations" on Sept. 15 and 16 in Washington, D.C. following the *2016 PDA/FDA Joint Regulatory Conference.*

As biosimilars become approved and available for patients, it will also be imperative for industry and regulators to ensure the same high level of science and quality for these products. PDA has worked to help establish processes and provide input on regulations in this area. This year, PDA will hold its inaugural *2016 PDA Biosimilars Conference* in Baltimore.

Finally, the world of ATMPs will require the same level of sound scientific collaboration to bring these innovative medicines to market. Development of guidances and standards will be required, regardless of type of ATMP. In this area, PDA will host its workshop, *Viral Safety of ATMPs* on June 6 in Berlin, followed by the *Advanced Therapy Medicinal Products* conference June 7–8.

Clearly, the prospects for biotech products are enormous. The role that PDA can play in advancing scientific risk-based approaches to these challenges through collaboration with industry and regulators makes this quite an exciting time to be involved! If you're interested in supporting PDA's biotech efforts, reach out to us via email at volunteer@pda.org.

[Editor's Note: PDA's Chair-Elect and BioAB member **Rebecca Devine** will offer additional insights into PDA's biotech activities in the next issue of the *PDA Letter* as well.**]**

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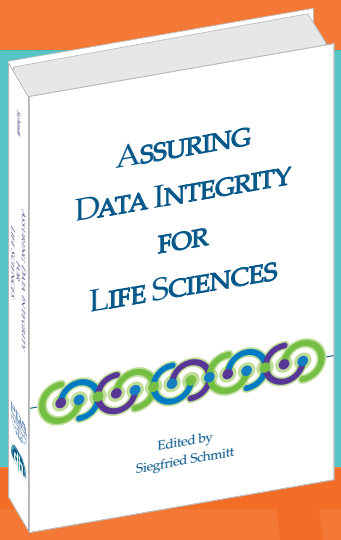

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SIEGFRIED SCHMITT, has more than 25 years of experience in a variety of roles from manufacturing, quality control and quality assurance to consulting on a wide range of products, processes and systems. He specializes in computerized systems compliance, is a fellow of the Royal Society of Chemistry, Chartered Chemist and Chartered Scientist, is published widely in various journals and has edited a number of journals and books. Siegfried is the current president of PDA's United Kingdom Chapter.

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editor's message

Lions and Tigers and Viruses, Oh My!

Many years ago I read the book *Beasts of the Earth: Animals, Humans, and Disease* by medical doctors **E. Fuller Torrey** and **Robert H. Yolken.** The authors argue that while our relationship with animals has led to many benefits, there remains a darker side to this relationship. Thanks to over 10,000 years of close living, animals have proved to be a source of microbes, frequently resulting in outbreaks of deadly diseases.

I thought about this book a lot while working on this issue, particularly the Infographic on page 30. All five of the viruses depicted in our "lineup" come from nonhuman animals. Due to industry's increasing reliance on mammalian cell lines, dangerous viruses can be introduced into production lines from raw materials taken from other species. Who would have thought that a disease affecting deer populations could contaminate a manufacturer's line of Chinese hamster ovary cells? Yet it has happened.

You need only look at recent virus outbreaks to understand the importance of effective viral clearance studies in our industry. Interestingly, most of the viruses behind these outbreaks originated in nonhuman animals. Ebola's origins lie in fruit bats. And the virus behind the latest pandemic, Zika, was originally identified in 1947 in a rhesus monkey. For all we know, it, too, originated in another animal species.

Now, as an animal lover, I hope I'm not scaring any of you from enjoying the company of animals. But these cases illustrate the importance of viral clearance studies in our industry as we rely more and more on cell lines derived from living organisms. For our cover story, PDA volunteers **Dayue Chen** and **Qi Chen** review the literature on the use of retentive filters in virus filtration (p. 20). **Sven Deutschmann** looks at PCR-based methods for detection of adventitious agents, including viruses (p. 26). In this issue's Science Snapshot, we also included a list of virus-oriented articles found among the Top 50 most-read *PDA Journal of Pharmaceutical Science and Technology* articles in February.

And don't forget to check out our latest *On the Issue* video on the *PDA Letter* website (https://www.pda.org/pda-letter-portal/multimedia/video). We recently posted Part 1 of our video interview with Merck's Manufacturing CIO **Michele D'Alessandro** on the convergence of IT and manufacturing.

Before I forget, I want to recognize those I met at this year's Annual Meeting in San Antonio a few weeks ago. For those new acquaintances, it was a pleasure meeting you. And for those who I've been acquainted with for awhile, I enjoyed meeting you once again at yet another lively Annual Meeting. I hope to see everyone again at next year's Annual Meeting in Anaheim. Who knows? Maybe by then I'll be a better dancer!

— **Rebecca Stauffer,** filling in for **Walter Morris** this issue.

PDA Letter

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

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

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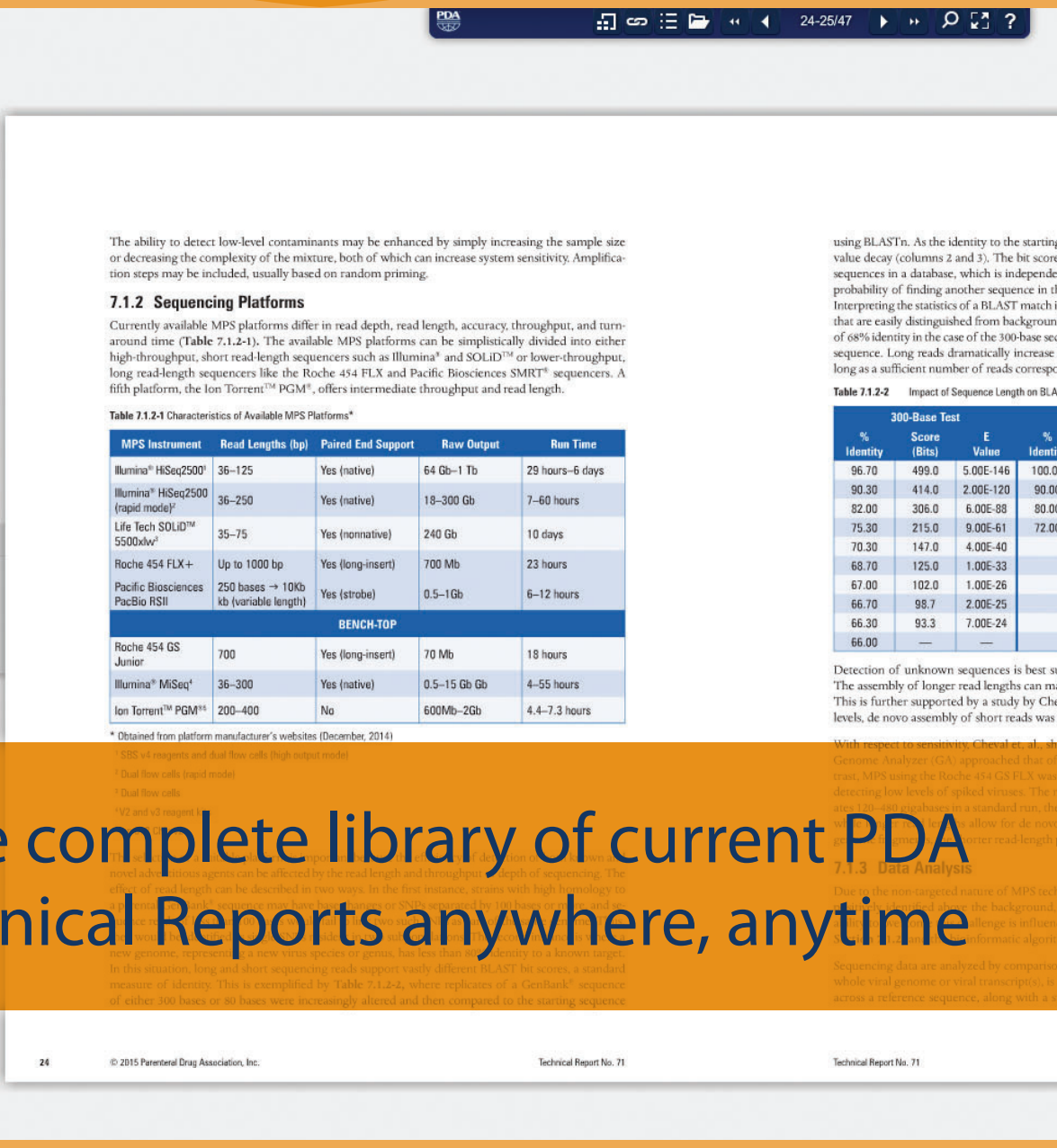

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