People • Science • Regulation

PDA Letter

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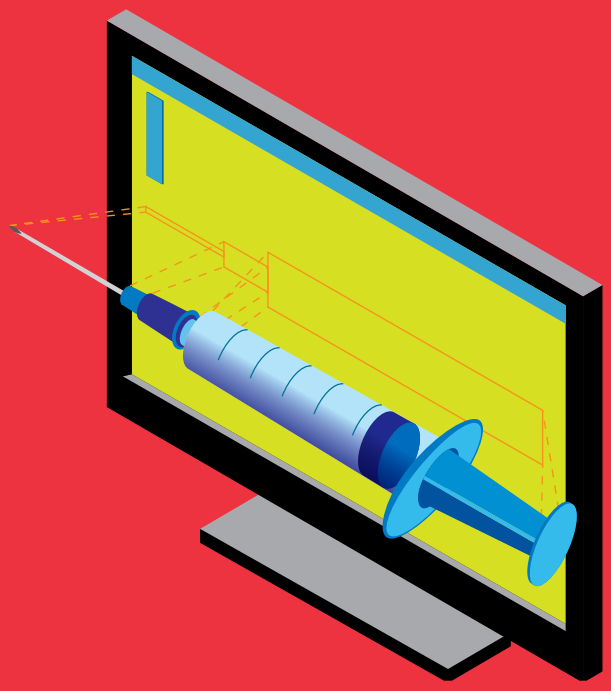

The Age of Pharma 4.0

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2019 SCHEDULE

OPTION 1
Week 1: January 28 – February 1
Week 2: February 25 – March 1

OPTION 2
Week 1: March 18-22
Week 2: April 15 -19

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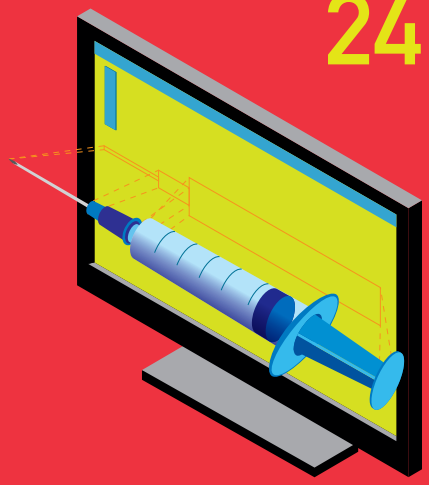
October 2018 PDA Letter



Big Data, Pharma 4.0 and Legacy Products

Jana Spes, Boston Biomedical, and Wayne Levin, Predictum

Big data offers companies a unique opportunity to close the knowledge gap that exists for legacy products and processes. Those companies that close this knowledge gap are better positioned to transform their manufacturing operations for Industry 4.0.

Cover Art Illustrated by Katja Yount

Big Data: The Panacea for Pharma's Ills?

Khan Lau, Promedica International

Two words are driving innovation within the pharmaceutical industry these days: "big data." Start-up companies like Datavant are receiving millions of dollars to harvest, organize, interpret and, hopefully, protect large amounts of data from a variety of stakeholders in the healthcare space.

InfoGraphic

Industry 4.0 in 3.0 Steps

Industry 4.0 has generated considerable buzz within pharmaceutical manufacturing but how can companies implement it?

PDA Letter

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

Subscriptions are not available.

Departments

Digital Exclusives

> **On the Issue** | Packaging Components: Extractable/Leachable Control
> The U.S. FDA's **Dan Mellon** provides the Agency's perspective on extractable and leachable control for packaging components.

> Industry Converges on Pharmacopeial Convergence
> Day 1 of the inaugural PDA Europe *Pharmacopoeia Conference* examined harmonization among the global pharmacopeias.

> A Deep Dive into Pharmacopeial Harmonization
> Presentations on Day 2 of the *Pharmacopoeia Conference* explored how industry can work together with the global pharmacopeias.

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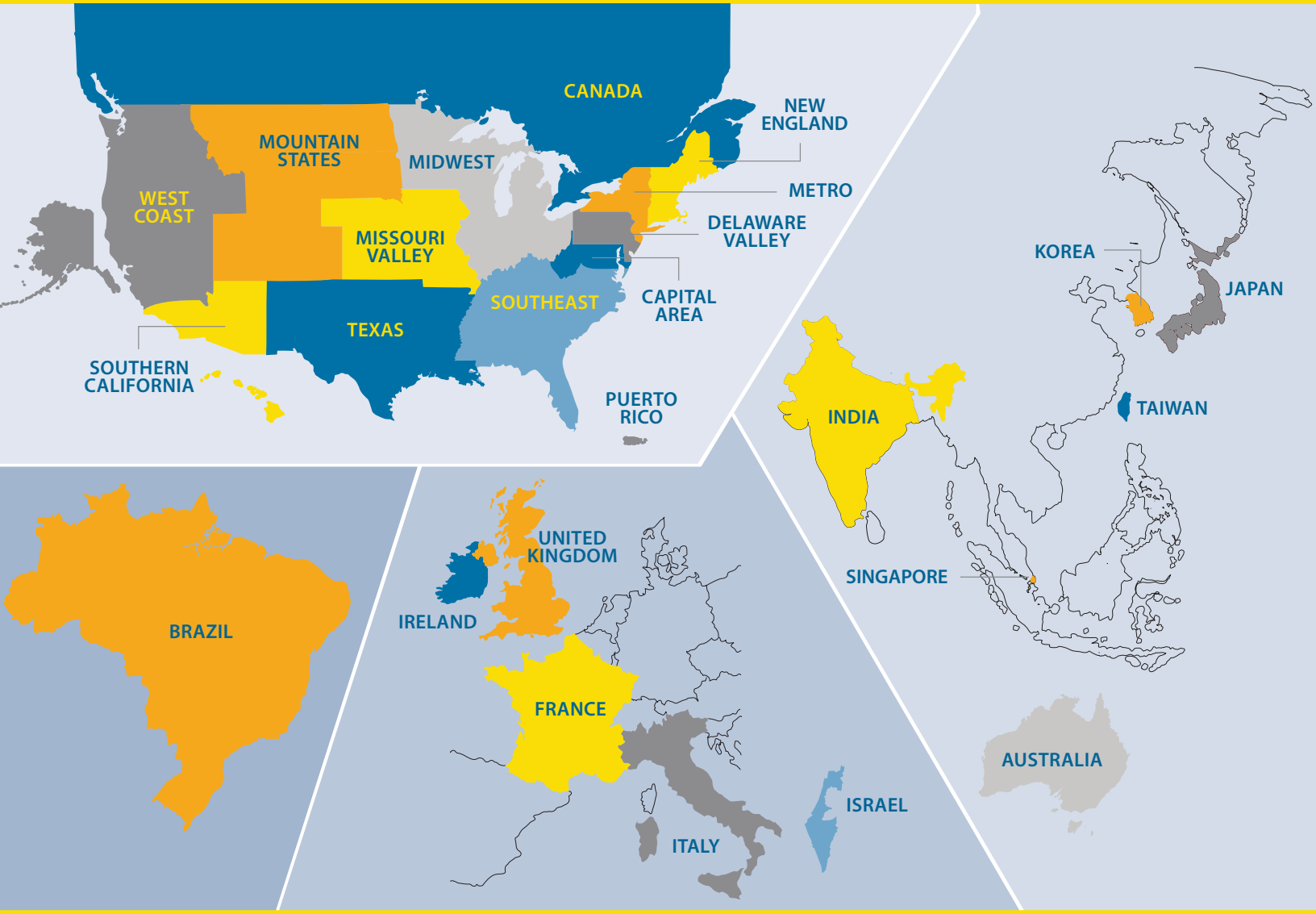
PDA Chapters

Your Local PDA Connection



Are you curious about the issues unique to your region?

Another layer of PDA leadership resides at the grassroots level in the Chapter organizations. Regional PDA Chapters provide local services to the membership, including translations of PDA publications, networking social events, student scholarship and annual regulatory and technical conferences. Each Chapter is managed by volunteer leaders.

Learn more about your local Chapter at www.pda.org/Chapters.

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PDA Letter 4.0?

One of the best parts about living in the Washington, D.C. area is being within easy reach of numerous museums covering a broad array of topics. One of my favorites is the Newseum. My favorite gallery features an 18th century Boston newspaper reporting the death of Blackbeard the pirate in heavy black text on yellowed parchment, complete with exceptionally gory illustrations — a story that was "breaking news" to the paper despite being several months old by the time of publication. Contrast this with the exhibition of the Conus 1 satellite truck, the world's first satellite newsgathering vehicle. Developed in 1984, this truck enabled local television stations to air live news reports instead of depending on networks for coverage. Quite the juxtaposition, indeed!

Rebecca Stauffer

I have that same feeling when I look at photos of parenteral manufacturing in the 1930s through the 1950s. In one particular photo that adorns a wall here at the PDA headquarters, rows of workers are seated next to each other—ungowned, with no barriers between them and the product. Certainly, unthinkable today. Also, think about this: there would have been no data about the production process until after a batch had been produced, perhaps not even for weeks or months. That data would also have resided on paper, which we all know can be damaged, lost or even altered.

But just like we can receive real-time news updates on our mobile devices, Industry 4.0 is enabling pharmaceutical manufacturers to learn about issues in the production process in real-time. Throw in automation and other new technologies and there are exciting changes ahead. PDA's Manufacturing Science and Operations Program (MSOP[SM]) team has been working to bring Industry 4.0 topics to the forefront of PDA's membership, including the *2018 PDA Manufacturing Intelligence Workshop* held in March. The many members of the MSOP I have met are all passionate about transforming current manufacturing processes for the better.

In previous columns, I have covered how the *PDA Letter* is following similar trends. I want to use this opportunity to remind readers that the Letter editorial team also publishes "digital exclusives" on our website that do not appear in print editions. Recent digital exclusive articles include a two-part summary of the 2018 PDA Europe *Pharmacopoeia Conference* ("Industry Converges on Pharmacopeial Convergence" and "A Deep Dive into Pharmacopeial Harmonization"), a look at how rapid monitoring and QRM can improve environmental monitoring ("Does QRM + RMM = Better EM?") and a case study on cryopreservation ("Evaluating Cell Viability After Cryopreservation"). Along with these articles, two recent "On the Issue" videos have spotlighted U.S. FDA regulators (**Dan Mellon,** "Packaging Components: Extractable/Leachable Control," and **Francis Godwin,** "Heparin Crisis: 10 Years Later").

Industry 4.0 will continue to be a topic discussed in the Letter and at PDA conferences around the world. Speaking of which, if you attend any PDA meetings in the D.C. area and have some extra time outside the meeting, I encourage you to visit some of our local museums, especially the Newseum.

Sprechen Sie Annex 1?

PDA will be hosting a German-language workshop on Annex 1 Dec. 11 in Berlin. This one-day workshop will cover the potential impact to industry from the Annex 1 changes. The opening session will feature talks from two regulators representing German states (**Beate Reutter** and **Andreas Schieweck**). The remainder of the workshop will consist of roundtable discussions on various Annex 1 revisions, including barrier systems, production of sterile products and steam.

For more information, visit www.pda.org/eu/annex2018.

Volunteers Needed for PDA Journal

The *PDA Journal of Pharmaceutical Sciences and Technology* is still looking for volunteers to join the Editorial Board or serve as peer reviewers. Experts with the following specialties are particularly needed: aseptic processing/sterilization, pharmaceutical and biopharmaceutical manufacturing science, supply chain, packaging science, drug delivery, pharmaceutical microbiology and viral clearance.

The Journal is currently accepting applications until volunteer positions have been filled. If interested, please forward a resume or CV to volunteer@pda.org.

Remember to Cast Your Vote!

All PDA members in good standing are eligible to vote for candidates for the 2019 Board of Directors. The election closes at 11:59 p.m. EST on Nov. 7. Members can vote online at www.pda.org/vote or at conferences in the United States and Europe prior to the closing date.

Information about the candidates can be found at the PDA website. Up to three candidates may be selected.

2019 Visual Inspection Forum Springs into Spring

Since its inception, PDA has hosted the annual *Visual Inspection Forum* in the fall. In 2019, this meeting moves to the spring. The 2019 *Visual Inspection Forum* will be held April 23–24 in Washington, D.C. To register, visit www.pda.org/2019visual.

PDA Volunteer Spotlight

Marc Hogreve

- **Senior Engineer Integrity Testing**
- ***Sartorius Stedim Biotech GmbH***
- Volunteer Since | **2012**
- Current City | **Barterode, Germany**

Do not ask yourself if you are able to do it; just do it

What has been your most memorable PDA experience to date?
Definitely the *2016 PDA Annual Meeting* in San Antonio, Texas, where I gave my first talk in front of a big audience ("Integrity Testing of Single-Use Bags and Bioreactors"). This experience helped me improve my presentation skills, allowing me to overcome my stage fright.

What led you to volunteer with PDA?
In 2015, I wanted to contribute to the revision of *PDA Technical Report No. 27: Pharmaceutical Package Integrity.* Since then, I have joined several other task forces developing best practices for integrity testing of single-use systems. I remain part of these groups and have also joined a few program planning committees. Additionally, I have taught a PDA Education course on container closure integrity.

Do you have any advice for new volunteers?
Do not ask yourself if you are able to do it; just do it. Every single volunteer activity helps support our industry in its mission to enhance the future of healthcare.

What inspired you to choose your current career path?
I wanted to help improve the performance of our single-use systems, so our customers can ensure patient safety and save human lives.

Who is your favorite musician?
Pink! I like her music, and, in my opinion, she is definitely one of the best artists in the world. Her shows are really incredible but, unfortunately, I have never had the chance to see one live.

PDA
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Southeast Chapter Meeting Pairs Wine, Decon Tech

John Groth, SKAN US

Decontamination plays a critical role in sterile drug product manufacturing. On Aug. 16, members of PDA's Southeast Chapter met in Raleigh, N.C., for an evening filled with product demos of advanced decontamination technologies and a complimentary wine tasting.

In light of the many customers who have benefited from deploying advanced decontamination technologies, SKAN US showcased some of the company's latest products in this space. By implementing these solutions, many customers have enjoyed higher production capabilities due to shorter cycle times.

During the meeting, vapor phase hydrogen peroxide was under considerable discussion. SKAN representatives demonstrated some of the newest products in this area, such as SKANFOG®, a novel nebulized hydrogen peroxide delivery system, and NANOX® catalyst technology, which offers quicker aeration times and reduced energy use.

By implementing these solutions, many customers have enjoyed higher production capabilities

Aside from product demos and discussion of decontamination concerns, there was still some fun to be had. The evening concluded with a wine tasting focused on the rosé wines of France. Attendees learned about the different types of grapes used to make it and how they affect the final product. **Maryse Schneider**, SKAN's resident microbiologist, provided some scientific insights into the wine tasting as her family runs a vineyard in, of course, France!

As the fun ended, SKAN representatives handed out fedoras and umbrellas, which ended up coming in handy due to the rainy North Carolina weather that month. SKAN appreciated the opportunity to showcase some new decontamination products for the Southeast Chapter and have fun at the same time.

PDA Who's Who

Maryse Schneider, Manger, MicrobioLab, SKAN

Pharmacy Student Sees Future of Pharma in Berlin

Aoife Clancy, Trinity College Dublin

This June, I was fortunate enough to be awarded a student bursary from PDA's Ireland Chapter to attend the *3rd PDA Europe Annual Meeting*. I was extremely excited to attend the event and learn about the current trends and emerging technologies within the global pharmaceutical community

On the first day of the conference, I received a warm welcome from the members of the Ireland Chapter attending the meeting. They introduced me to their colleagues and other conference attendees. I eagerly learned about the roles which they assumed in their respective companies.

The theme of the meeting, "Global Healthcare of the Present and Future," was of great interest to me, given my background in pharmacy. The meeting consisted of presentations from regulatory, industry and technology representatives around the world. Since a lot of my experience comes from patient-facing roles, the talks covering patient perspectives, personalized medicines and patient centricity greatly appealed to me. The "Young Professionals in PDA" session on Day 2 was definitely a highlight of the meeting. **Cristoph Marschall,** who also completed an undergraduate degree in pharmacy, presented on protein powder suspensions and their viability as an alternative to conventional formulations. He touched on the problems associated with proteins due to their potential to aggregate, causing conformational changes. Marschall also discussed the issue of viscosity with nonaqueous formulations, which can present challenges during the injection process. I could really connect with this topic, having completed relevant modules during my time at Trinity College. Finally, **Reyk Horland's** talk on multiorgan chip technologies in the closing plenary was very inspiring. It was exciting to hear about the ways in which safety and efficacy data can be generated much earlier in the drug development timeline.

To compliment the fantastic presentations at the meeting, the networking event on the first night afforded me with a memorable tour of Berlin. We embarked on a cruise through the channels of the city—a novel way to see the sights. This is a memory I will never forget.

I would like to extend my sincere thanks to the Ireland Chapter for awarding me the student bursary and providing me with an amazing opportunity to attend the *3rd PDA Europe Annual Meeting*. I learned so much, met so many incredible people and found career inspiration.

The author takes in the Berlin scenery on the networking cruise

PDA Who's Who

Reyk Horland, Vice President, Business Development, TissUse

Cristoph Marschall, Ludwig-Maximilians-University

Meet the *PDA Letter's* First Intern

Aneeta Mathur-Ashton, American University

Hello, my name is **Aneeta Mathur-Ashton** and I served as the Publishing Intern for PDA during the summer of 2018. In this role, I assisted Managing Editor **Rebecca Stauffer** in putting together the July/August issue of the *PDA Letter.* For the most part, I spent my time copy editing articles sent from authors around the world. I also got a chance to see how a magazine is put together by sitting in on various planning meetings, and I watched how they created a comprehensive "map" of an issue, outlining articles slated to appear. This map hangs in Rebecca's office.

Rebecca and I also sat together to edit certain articles, which proved to be very beneficial, giving me another person to collaborate with. We interviewed some members of various pharmaceutical companies together, which allowed me to hone my interviewing skills. I completed numerous research assignments, including one where I looked up information about the impact of natural disasters on the pharmaceutical supply chain—this research resulted in the July/August infographic (p. 48), "The Dominoes of Natural Disasters."

As a journalism major at American University who has spent the last five years as a student journalist, this internship turned out to be a perfect fit. It taught me a lot about myself as a journalist and as a writer. The biggest benefit? I had the opportunity to strengthen my copy editing skills. All journalists are required to master basic copy editing and adhere to *Associated Press* style rules. This internship gave me the opportunity to flex the editing skills that I already had while also enhancing them. I became more aware of grammar rules and found it easier to revise sentences. In addition to flexing my grammar muscle, I also grew my scientific expertise, on which I can draw for future career endeavors.

Aneeta assisted Rebecca in filling out the *PDA Letter* map that guides each issue

Going forward, I plan to use the skills I developed from my PDA internship to make me a better writer. When I return to working on the American University student newspaper, I intend to use my strengthened skills as a copy editor when editing the work of other reporters. And I plan to use my strengthened knowledge of AP style to enhance the writing on my next newspaper article.

Spending my summer with PDA was one of the best decisions I have made since entering college. I would highly recommend this opportunity to any college student who is interested.

Marketing Your Postgraduate Degree to Employers

Tamer Helmy, PhD, Independent Consultant

Jobseekers with postgraduate degrees are often challenged when translating their academic backgrounds to industry employers, often due to misconceptions of what graduate studies entail and the skills they provide. In my opinion, professionals holding postgraduate degrees generally do not market their degrees very well.

These specialized jobseekers need to address three questions to achieve success in their job hunts: 1) What are the transferable skills that can be provided by a graduate degree to industry? 2) Why have industries grown resistant to higher education? 3) How can I address misconceptions?

1. What are the Transferable Skills?

The answer to the first question crosses all professions. The focus should be on the skills acquired by pursuing higher education.

First, we should consider every person who earns a graduate degree a hero. They decided to hone their skills beyond a bachelor's degree into a particular specialty, often sacrificing opportunities to enter the job market right away.

And think about this, according to the Council of Graduate Schools, the completion rate for postgraduate degrees has been about 50–60% in the last few years ***(1,2).*** In other words, half of the people who enter graduate programs do not finish. It is not an easy task; it requires tenacity as well as monetary and personal sacrifices. Individuals who delve into this process and manage to accomplish it have already proven they can succeed on a big project. Consider them project managers in a sense. These project managers are responsible for budgeting, data collection, conducting a novel research idea, critically thinking about the current methods used in the industry and trying to improve industry practices.

Finally, most graduate degrees require a final project that has to be expertly written, critiqued by peers and specialists and presented. These skills are essential to success in any business.

Jobseekers with newly minted graduate degrees must communicate these transferable skills to potential employers.

2. Why the Resistance?

There are many reasons some employers are reluctant to hire postgraduates. This could be, in part, due to comedies that tap into the stereotype of socially awkward scientists such as those portrayed in *The Nutty Professor* or *The Big Bang Theory*. I completely agree that at least 50% all the scientists I have met are socially awkward—but so is most of the entire human population.

Another unfortunate misconception is that highly educated individuals are seen as expensive, independent thinkers. But is this not required for success? Add to this, that they are also often held to higher, unrealistic standards. For example, I remember when I was at Arizona State University, someone's relative gave him a rock and, this being a biologist doctorate student, asked him to identify it. The poor guy did not know what to do other than seek help. How can you explain to your relative that biology is different from geology, let alone that you, as a scientist, do not know everything about everything?

3. How to Address Misconceptions?

The burden is on postgraduate jobseekers to explain why their advanced degrees are relevant and how can they help benefit employers. Those postgraduates who have achieved industry success, in my opinion, have a moral obligation to advise these jobseekers trying to enter their fields. Higher education institutions should continue to improve their outreach to industries. Industry employers, on the other hand, should consider jobseekers with graduate degrees as highly qualified people who can think outside the box.

Yet, in spite of these "shoulds," the onus is on graduate degree holders to sell their degrees to employers. A graduate degree is a valuable asset that needs marketing. Graduating with a master's or a doctoral degree is not a guarantee of finding a good job, nor does it speak for itself. People with graduate degrees should strive to promote their skills and continue to be open to learning more, as they have always done.

[Editor's Note: A version of this article first appeared on the author's personal LinkedIn page**.]**

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1. "The Crucial Issue of Doctoral Non-completion." *Council of Graduate Schools*. https://cgsnet.org (2007) https://cgsnet.org/cgs-occasional-paper-series/university-georgia/chapter-1 (accessed Sept. 4, 2018)
2. Council of Graduate Schools. *Ph.D. Completion*

Continued at bottom of page 19

Not So Different After All

Compounding Pharmacist Learns about Aseptic cGMP in PDA Education Course

Rebecca Stauffer, PDA

Earlier this year, ***Rick Rhoads,*** *PharmD, a pharmacist with a compounding pharmacy, attended PDA's "Aseptic Processing Training Program." Below he shares his experience with the* PDA Letter *and what he thinks compounding pharmacists can gain from the course.*

PDA Letter: **Tell us a little bit about your background.**

Rhoads: For the past 11 years, I have worked as a compounding pharmacist at University Compounding Pharmacy, where we provide custom sterile and nonsterile medications directly to patients with a patient-specific prescription. Working in a compounding pharmacy has provided me with opportunities to gain a wide range of experience. In the past, I have worked in sterile processing, facility design, quality management, personnel training, regulatory compliance and other areas. I currently serve as the Director of Compounding, responsible for regulatory compliance, development of the quality system and leadership advancement.

Recent growth has allowed us to differentiate our 75 employees into specialized teams to respond to changes in our industry. In many ways, the regulatory landscape is becoming more complex. Traditionally, pharmacy compounding has been regulated by the states, meaning each state has a different set of regulations. But in the last five years, these laws have changed due to the compounding tragedy at the New England Compounding Center. The U.S. FDA also began regularly inspecting compounding pharmacies about five years ago. We are just learning what FDA oversight of compounding looks like, and how to remain compliant. This complicates matters for our pharmacy even more because we have licenses in 41 different states.

PDA Letter: **As a pharmacy compounder, what drew you to PDA and, by extension, to the "Aseptic Processing Training Program?"**

Rhoads: In 2015, our pharmacy received its first FDA inspection, for which I was completely underprepared. I focused on complying with USP <797> Pharmaceutical Compounding – Sterile Preparations, the USP chapter for sterile compounding. The FDA investigator, however, approached it from a cGMP perspective. The requirements, and even terminology used in cGMP, are different than those used in compounding. By the end of the inspection, I was convinced that learning cGMPs from an aseptic manufacturing point of view was important, both from a quality and a regulatory standpoint. Since 2016, I have attended two classes at PDA and each one provided a new perspective for me. My first aseptic training was the "Recommended Practices for Manual Aseptic Processing." Subsequently, I attended the two-week "Aseptic Processing Training Program." **David Matsuhiro** and the rest of the instructors provided a wealth of very practical information.

PDA Letter: **From your experience, what are the main differences between pharmacy compounding and cGMP? How about similarities?**

Rhoads: Aseptic manufacturing and compounding pharmacies serve very different roles in healthcare. Traditional compounders prepare small batches of medication that are dispensed directly to patients. These medications are not FDA approved. Whether it is an IV in a hospital or a custom capsule in a retail pharmacy, the finished dosage form is not available from a manufacturer. And due to the critical nature and limited availability, compounders must supply these medications in a timely manner. In many cases, that the patient receives therapy immediately is crucial. Quality decisions are very different between the two industries as well. The risk associated with compounding a drug used by one patient over ten days is much lower than

the risks in manufacturing 50,000 vials for distribution over the course of a year. Consequently, compounders tend to rely more heavily on quality standards while manufacturers rely on quality systems. There are limits to this analogy, however. Many pharmacies now make large batches of medication, which requires a better quality system. In my opinion, the challenge for compounders is to apply the strict controls of a pharmaceutical quality system to a pharmacy operation to meet the diverse, critical needs of patients.

As far as similarities, pharmaceutical manufacturing initially emerged from pharmacy compounding. The goal of both industries is to provide safe and effective medications that treat disease and promote health. The safety of medications used by the public is imperative, regardless of whether they were manufactured or compounded. Many of the same principles are translatable between aseptic manufacturing and sterile compounding. Whether it is facility design, aseptic technique, gowning, or environmental monitoring, both industries are heavily focused on these aspects of their operation. Still, there is definitely a much higher standard in manufacturing. Manufacturing also has a more sophisticated understanding of how each of these elements fits into systems. In addition, the validation work is more robust.

PDA Letter: **What were the top three things you learned from the course?**

Rhoads: The first and most important lesson for our pharmacy was the pre-eminence of airflow in an aseptic operation. The airflow must dictate, on a minute level, every process involved in sterile compounding. This was not a completely new concept, but it was presented in a way that displayed the impact on the final product. For pharmacists, we typically perform aseptic manipulations in a unidirectional airflow device, like an LAFW or BSC. The setup and manipulations are performed in the same direct compounding area. This makes airflow principles for process design even more critical.

The next important concept was the lifecycle approach to validation. Intense validation work is not typically encountered in a compounding pharmacy because it is difficult to do this with thousands of different formulas. But one can adopt the concepts outlined and apply them to areas of high volume and high risk.

Finally, the important role of risk management in quality decisions is a concept we can better integrate in the pharmacy. **Hal Baseman** presented several comprehensive approaches to quality risk management (QRM). Compounders often make risk-based decisions without structured methods to evaluate them. To improve our quality risk management, we plan on utilizing a simplified QRM model presented by Hal.

PDA Letter: **How will this course help you going forward?**

Rhoads: During the course, it was easy to get overloaded with material. I wrote down lists of helpful information, but then distilled my notes down to large, impactful concepts. These concepts provide something of a guiding light for improving quality in the long run. As our pharmacy continues to grow, it becomes imperative to learn from the manufacturing industry. My goal is to bring the pharmacy as close to cGMP as possible, while maintaining the ability to serve the critical needs of patients. There is no doubt that the "Aseptic Processing Training Program" will help in this regard.

PDA Letter: **How could other compounders benefit from joining PDA?**

Rhoads: There is no better way to improve at something than by learning from those at a higher level than you. Out of necessity, cGMP manufacturers have better "built in" quality because their impact is so much greater. Compounders do not need to reinvent the wheel. The experts at PDA provide very useful information that is beneficial for compounding pharmacies wanting to take their operation to the next level. Joining and receiving training at PDA can be a good supplement for any compounding pharmacy serious about improving quality.

SNAPShot

New PDA Team Seeks to Improve Operations Metrics

Ramesh Tharuvai, Neurocrine Biosciences, Inc

Operational metrics are critical for evaluating, sustaining and improving the performance of a manufacturing operation. Common examples of operational metrics include schedule adherence, cycle time, yield, reject rate and loss for each unit operation. The way metrics are chosen, defined and used varies greatly across the biopharmaceutical industry. PDA believes that the industry could benefit from suggestions related to the identification, definition and use of operational metrics. With this in mind, in late 2016, PDA's Manufacturing Science and Operations Program (MSOP[SM]) established a small cross-industry operational metrics team to discuss how metrics can be used to improve operations on the shop floor, at the manufacturing site and across the globe.

The operational metrics team includes members from Eli Lilly, Genentech/Roche, Merck, Neurocrine Biosciences and Sanofi, representing expertise in drug substance, drug product, device assembly, packaging, operational excellence, continuous improvement and supply chain. In 2017, the group conducted an all-day benchmarking workshop at Genentech/Roche that addressed such concerns as the definition of metrics, their use in driving improvement, and the pitfalls and benefits of using them—all in the context of real-world examples spanning segments of the biopharmaceutical the industry.

The initial set of metrics targeted in the workshop consisted of overall equipment effectiveness (OEE), yield and cycle time. Key outputs from the benchmarking workshop include a compilation of best practices and approaches to using metrics to drive performance. Some examples of the insights from the workshop are: (1) OEE trending has been successful in driving benefits from better line uptime to better assay selection, and (2) using a balanced scorecard with "competing" metrics can help counteract behaviors that can otherwise result from focusing on a single key performance indicator. The group also reached a shared understanding of challenges in using metrics and how to overcome them, such as the visibility of metrics related to contract manufacturing, or the way yield indicators are defined in drug substance processes (either batch or perfusion) compared to drug product manufacturing.

In 2018, the operational metrics team has continued to work under the guidance of the MSOP[SM] to address additional metrics such as schedule adherence, end-to-end cycle time, reliability and employee engagement. The 2018 action plan developed by the team includes a variety of outreach efforts to engage internally within PDA and across the industry as a whole through benchmarking. The ultimate intent is to share the outputs of the operational metrics team with PDA membership in ways that make them useful, relevant and practical. In the meantime, the operational metrics team is actively looking for additional participation from the PDA member community and is exploring ways to incorporate member feedback into its efforts.

Journal *Top 10*

Below are the top ten articles from the *PDA Journal of Pharmaceutical Science and Technology* (journal.pda.org) for the month of August.

1. *PDA Paper*
"PDA Points to Consider: Best Practices for Document/Data Management and Control and Preparing for Data Integrity Inspections"

2. *Review*
"Particulate Matter in Injectable Drug Products"

3. *PDA Paper*
"Industry Perspective on the Medical Risk of Visible Particles in Injectable Drug Products"

4. *Conference Proceeding*
"Role of Risk Assessments in Viral Safety: An FDA Perspective"

5. *Research*
"Vapor Phase Hydrogen Peroxide Decontamination or Sanitization of an Isolator for Aseptic Filling of Monoclonal Antibody Drug Product—Hydrogen Peroxide Uptake and Impact on Protein Quality"

6. *PQRI Special Section* – Review
"The Product Quality Research Institute (PQRI) Leachables and Extractables Working Group Initiatives for Parenteral and Ophthalmic Drug Product (PODP)"

7. *PQRI Special Section* – Research
"Extractables Characterization for Five Materials of Construction Representative of Packaging Systems Used for Parenteral and Ophthalmic Drug Products"

8. *Research*
"Sealing Behaviour of Container Closure Systems under Frozen Storage Conditions: Nonlinear Finite Element Simulation of Serum Rubber Stoppers"

9. *Technology/Application*
"Ozone Generation during High-Voltage Leak Detection: Fiction or Reality?"

10. *Research*
"Determination of the Acceptable Ambient Light Exposure during Drug Product Manufacturing for Long-Term Stability of Monoclonal Antibodies"

Build Your CCI Knowledge Base Through Data, Tech

Jaime Cobo, WILCO AG

Recent regulatory and compendial updates emphasize the importance of gaining full knowledge about our manufacturing processes. The more information and knowledge we have about our processes and products, the more control tools might need to be introduced to achieve the expected quality of our products. The draft version of the EU Annex 1 revision emphasizes the use of quality risk management (QRM) principles to prevent microbial contamination in the final product. In other words, the collection of records/data from our processes is the way to gain more knowledge about our processes. Within this context, USP <1207> Sterile Product Packaging—Integrity Evaluation supports Annex 1 by describing and recommending the technologies to support container closure inspection purposes.

Considering the holistic approach, package integrity should be assured during the three product lifecycle phases: package development, process and assembly (the first phase); product manufacturing (the second phase) and commercial product stability (the third phase). Throughout this process, product sterility should be maintained until time of use with patient safety as the final goal.

In the first phase, during package development, helium mass spectrometry or headspace analysis might be selected for container closure integrity purposes but, for the second phase, vacuum decay, pressure decay, high voltage or mass extraction might be selected for container closure integrity testing.

The leakage rate to be measured in the product lifecycle phases varies based on the selected container closure technology and the product package risk assessment. For example, in the first phase, leakage rates of 1×10^{-7} mbar*l/s are expected to be measured while in the third phase, the leak testing method must detect a leakage rate of approximately 2.67×10^{-2} mbar*l/s (representing a 10 µm leak size @ 1,000 mbar differential pressure).

Keep in mind, there is no single universal container closure integrity technology available to test all kinds of containers, filled with any type of product and applicable for all product lifecycle phases. Additionally, selection of inspection technology should be based on the specification for each container and closure system for the specific product. Nondestructive deterministic technologies are the preferred technologies because they obtain a quantitative measurement.

Inspection technology also depends on the "personality" of the company in question. These "personalities" consist of those companies that are "beyond compliance," those that "comply with wide process, product knowledge and data" and those that "comply with limited process and product knowledge." The actual trend within those pharmaceutical companies "beyond compliance" is to design a flexible technical solution to test all products, using a combination of different, nondestructive testing technologies in one platform.

Besides the implementation of 100% container closure integrity testing on glass and plastic ampoules closed by fusion, the introduction of 100% container closure integrity testing on freeze-dried vials is becoming a common practice through application of a headspace analysis.

In summary, the actual requirements are based on gaining data from our processes, and to know, understand and monitor any improvement to conserve the integrity of the products throughout the complete product lifecycle. Nondestructive deterministic technologies are available in the market to monitor container closure integrity, either as a sampling approach or as an in-line application.

[Editor's Note: This is a summary of the author's talk at the *2018 PDA Biopharmaceuticals Conference* held April 17–18 in South Korea**.]**

About the Author

Jaime Cobo has worked for more than 12 years in the pharmaceutical and food industries, with experience in process improvements and inspection technologies. In his current role, he leads the sales department from WILCO AG.

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and Attrition: Analysis of Baseline Demographic Data from the Ph.D. Completion Project. http://www.phdcompletion.org/information/executive_summary_demographics_book_ii.pdf (accessed Sept. 4, 201

About the Author

Tamer Helmy is an independent pharmaceutical consultant and *PDA Letter* Editorial Committee member. He is a quality expert with more than 20 years of microbiology and aseptic processing experience.

Exciting New Changes are Coming to Pharma

Are You Prepared?

Melissa Seymour, Biogen, Inc., and Ghada Haddad, Merck & Co./ Merck Sharp & Dohme

Today's pharmaceutical industry is poised for breakthroughs that will change the way we think about medicine. From genetics to immunology, nanotechnology to predictive analytics, blockchain to bionics—the way we work is changing drastically. Even so, it is critical that existing medicines continue to be provided efficiently and effectively.

As an industry, we must both embrace significant change and continue to improve upon the medicines that patients so desperately need.

PDA has been at the forefront of continuous innovation in the pharma industry for decades. Through its flagship annual meeting, PDA provides a venue for obtaining current and wide-ranging information on topics related to innovative manufacturing and supply chain technologies.

The *2019 PDA Annual Meeting* will provide continued guidance on existing facilities and manufacturing processes and enhancing awareness of new therapies that will drive the future of the pharmaceutical industry. The opening plenary session will focus on the patient, providing a human face on the importance of driving novel medicines.

Plenary sessions will focus on the key aspects of our work including innovative manufacturing strategies, supply chain complexity, disruptive technologies and rapid drug development.

Concurrent sessions, as usual, will allow participants to choose topics important to their individual needs. These will address inventory segmentation, blockchain technologies, serialization, post-approval changes and risk management. Different manufacturing processes, including small molecule, biopharmaceutical and cell and gene therapies, will also be covered. Presentations in these sessions will provide a closer look at the advancements shaping our industry now and in the future.

2019 PDA Annual Meeting

San Diego
March 11–15
www.pda.org/2019annual

New Perspectives on Freeze-Drying

Thomas Beutler, GEA, and Yves Mayeresse, GSK

Freeze-drying technology has been constantly evolving. In terms of validation, quality-by-design (QbD) has replaced the classical approach to increasing product knowledge. With QbD, a design space can be defined in which the process can vary without impacting the critical quality attributes of the product.

The next advancement will be to develop a dynamic system, one able to give information on sublimation and product temperature evolution during the cycle, to replace the static system. In terms of validation, a commonly used strategy is one in which the heat transfer coefficient for the device and the freeze-dryer is determined. The resistance of the product is measured, and freeze-dryer capability monitored to avoid chocked flow. With those three elements, the scale-up and transfer of product is no longer empirical but can be predicted. The sensors able to monitor the cycle are also evolving. For example, a mass spectrometer can be installed on a freeze-dryer that uses wireless probes to determine potential leakage of silicone oil. This tool can also monitor the end point of primary drying.

In the past, refrigerants were improved to avoid ozone depletion, but they still have a high potential to contribute to global warming. The 2015 F-gas regulation targets cutting these emissions in the United States by two-thirds by 2030, and the first major reduction has recently come into force. In 2018, the distributor may sell only refrigerants with a CO2 equivalent to 63% of the 2015 level. Consequently, the race is on to find new refrigerants for freeze-dryers before the supply runs out. Fortunately, an alternative is arising in some companies.

These topics and others will be discussed during the next PDA Europe *Pharmaceutical Freeze Drying Technology* conference at the end of November.

Pharmaceutical Freeze Drying Technology

Seville, Spain
Nov. 27–28
www.pda.org/EU/FreezeDrying2018

2018 PDA Upcoming Events

SAVE THE DATE for PDA's 2018 Events

OCTOBER

15-16
PDA Europe Pharmaceutical Microbiology Conference
Berlin, Germany
pda.org/EU/PharmaMicro

15-17
13th Annual PDA Global Conference on Pharmaceutical Microbiology
Bethesda, MD
pda.org/2018Micro

17-18
2018 PDA Endotoxins Workshop
Bethesda, MD
pda.org/2018Endotoxins

17-18
Best Practices and Points to Consider in Aseptic Processing
Berlin, Germany
pda.org/EU/BP-Aseptic2018

17-18
Mastering Challenges of Data Integrity and Computer System Validation
Berlin, Germany
pda.org/EU/MasteringDI

17-18
Rapid Microbiological Methods
Berlin, Germany
pda.org/EU/RMM2018

17-18
Environmental Monitoring and Contamination Control
Berlin, Germany
pda.org/EU/EMCC18

18-19
13th Annual PDA Global Conference on Pharmaceutical Microbiology Course Series
North Bethesda, MD
pda.org/2018MicroCourses

22-25
SOLD OUT
■ **Filtration Processes in the Pharmaceutical and Biopharmaceutical Industry**
Bethesda, MD
pda.org/2018Filtration

23-24
2018 PDA Cell and Gene Therapy Conference
Bethesda, MD
pda.org/2018CGT

23-24
Visual Inspection Forum
Berlin, Germany
pda.org/EU/VIF2018

23-25
SOLD OUT
■ **Airflow Visualization Techniques and Practices – Option 2**
Bethesda, MD
pda.org/2018OctAir

25-26
An Introduction to Visual Inspection: A hands-on course
Berlin, Germany
pda.org/EU/IVI2018

25-26
Einfache und Prozessorientierte Qualifizierung
Berlin, Germany
pda.org/EU/EPQ2018

25-26
Mastering Automated Visual Inspection
Berlin, Germany
pda.org/EU/mavi2018

29-2
PDA Validation Course Series
Bethesda, MD
pda.org/2018VCS

30-31
2018 PDA Annual Singapore Conference
Singapore, Singapore
pda.org/2018Singapore

NOVEMBER

1
2018 PDA Designing A Risk-Based Cleaning and Disinfection Program for Pharmaceutical, Biotech, and Medical Device Facilities Training Course
Singapore, Singapore
pda.org/2018RBCSingapore

1-2
Analytical Method Qualification Validation, Verification, and Transfer for Biotechnological Products
Bethesda, MD
pda.org/2018AMQV

1-2
Quality Culture Assessment Tool and Training
Singapore, Singapore
pda.org/2018SingaporeQCT

5-8
Quality Risk Management Certificate Program
Bethesda, MD
pda.org/2018QRM

6-7
2018 PDA Taiwan Conference
Taipei, Taiwan
pda.org/2018Taiwan

6-7
Outsourcing and Supply Chain – A 360° View
Seville, Spain
pda.org/EU/2018Outsourcing

6-8
■ **Validation of Moist Heat Sterilization Processes**
Bethesda, MD
pda.org/2018NovVMH

8-9
2018 PDA Taiwan Course Series
Taipei, Taiwan
pda.org/2018TaiwanCourses

8-9
Practical Guide for Root Cause Investigations – Methodology & Took Kit
Seville, Spain
pda.org/EU/rootcause2018

8-9
Risk Management in Technology Transfer
Seville, Spain
pda.org/EU/risk-tt-18

13-15
■ **PDA Environmental Monitoring Course Series**
Bethesda, MD
pda.org/2018NovEMCS

Denotes laboratory courses taught in Europe. | ■ This course is taught in PDA's U.S. manufacturing training facility.

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

15-16
■ **Single Use Systems for the Manufacturing of Parenteral Products**
Bethesda, MD
pda.org/2018SUS

22
Project Management in the Pharmaceutical Industry – Challenges and Possibilities
Berlin, Germany
pda.rog/EU/PM2018

27-28
Pharmaceutical Freeze Drying Technology
Seville, Spain
pda.org/EU/FreezeDrying2018

27-28
11th Workshop on Monoclonal Antibodies
Seville, Spain
pda.org/EU/MABS2018

29
Application of a Risk-Based Approach to Freeze-Drying Processes
Seville, Spain
pda.org/EU/RBP2018

29-30
Development of a Freeze-Drying Process
Seville, Spain
pda.org/EU/FDProcess2018

29-30
Extractables & Leachables
Seville, Spain
pda.org/EU/E-and-L2018

29-30
CMC Regulatory Compliance for Biopharmaceuticals
Seville, Spain
pda.org/EU/cmc-regulatory2018

DECEMBER

3-6
Fundamentals of Aseptic Processing – Option 5
Bethesda, MD
pda.org/2018DECFundAP

7
NEW COURSE
Assay Validation by Design
Bethesda, MD
pda.org/2018Assay

10-12
NEW COURSE
Quality Risk Management Facilitator Training
Bethesda, MD
pda.org/2018Facilitator

11
PRESENTED IN GERMAN
Annex 1 Workshop
Berlin, Germany
pda.org/EU/Annex1_Berlin

13
NEW COURSE
Passive Thermal Protection Systems for Global Distribution: Qualification and Operational Guidance
Bethesda, MD
pda.org/2018Thermal

PLAN AHEAD FOR 2019

Registration is now open for PDA's 2019 Signature Events

MARCH

11-13
2019 PDA Annual Meeting
San Diego, CA | *pda.org/2019Annual*

APRIL

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

MAY

16-17
Pharmacopoeia Conference
European Location Coming Soon | *pda.org/EU/pharma2019*

JUNE

25-26
4th PDA Europe Annual Meeting
Amsterdam, The Netherlands | *pda.org/EU/Annual2019*

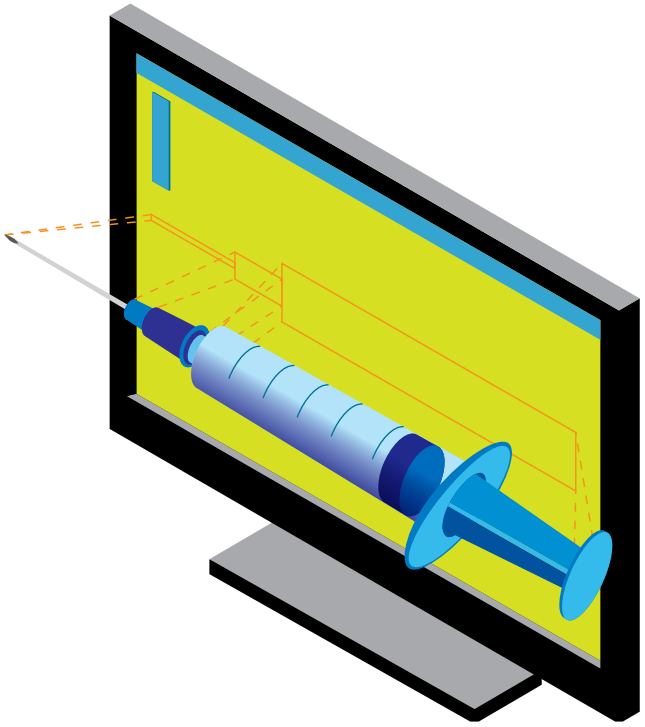
OCTOBER

21-23
14th Annual PDA Global Conference on Pharmaceutical Microbiology
Bethesda, MD | *pda.org/2019Micro*

22-23
2019 PDA Universe of Pre-Filled Syringes and Injection Devices
Gothenburg, Sweden | *pda.org/EU/2019UPS*

Big Data, Pharma 4.0 and Legacy Products

Jana Spes, Boston Biomedical, and Wayne Levin, Predictum



Article at a Glance

- The first steps in closing knowledge gaps for legacy products are critical
- Numerous methodologies are available for dataset assessments
- Analyses can be automated

A review of quality deviations helps identify failure modes

Big data offers companies a unique opportunity to close the knowledge gap that exists for legacy products and processes. Companies that close this knowledge gap are better positioned to transform their manufacturing operations to take advantage of Industry 4.0.

Industry 4.0, it is said, will create "smart factories" and make systems more flexible to customize mass manufactured products—points reflective of pharmaceutical industry trends toward increased efficiency and personalized medicine ***(1–3).*** In these systems, information is shared by leveraging cloud-based systems to use key data for strategic decision-making and enable continuous improvement with a goal to move beyond compliance.

"Pharma 4.0," a term used to describe Industry 4.0 specific to pharmaceutical manufacturing settings, underscores the need for pharmaceutical manufacturing to be driven **by process requirements**. A manufacturing plant set up according to Pharma 4.0 principles consists of machines, equipment and computers that constantly monitor every aspect of the process via multiple sensors, including their own wear and tear ***(1).***

Yet before big data analytics can be deployed, companies need to close process knowledge gaps for legacy products and define how to balance analytics with subject matter expertise.

A recent study looked at how to improve process knowledge and set foundations for big data applications. This particular study can be extended to any portfolio with complex manufacturing processes commercialized over the last decades. The takeaways from this study are outlined below.

Building Blocks, Definitions and CQAs

First, a company must select a methodology to characterize legacy processes and determine sources of data from the ever-expanding options. This can be outlined in the project charter. Holistic and integrated use of data is essential for repeating the results of analysis, transferring information to other products and augmenting regulatory filings.

Next, the project team should identify material attributes, process parameters and other variables (e.g., mixing of batches, hold times) that may impact product critical quality attributes (CQAs) over the shelf life according to quality-by-design principles. Information can be extracted from the continued process verification (CPV) program, annual product reviews, investigations, risk assessments, batch records, and development reports. The initial cause-and-effects matrix (CEM) needs to be detailed thoroughly and a comprehensive risk assessment, using such recognized methods as failure mode effect analysis (FMEA) conducted per ICH Q8–Q9 ***(4,5).*** A review of quality deviations helps identify failure modes that could be otherwise missed. The FMEA points to areas with the highest potential for failure **(Figure 1).** Aggregated risk assessment results in **Figure 1** show which unit operations have the most and highest-scored risks. The project team should set the threshold for the risk priority number (RPN) and aim to improve controls for these areas, bringing the RPN to an acceptable level.

The scope should aim to fill knowledge gaps exposed by the CEM and FMEA. For products with multistep, complex processes, the recommended strategy is to first characterize the critical and less understood steps (e.g., mixing or coating steps for dosages with controlled release dissolution profiles, pH adjustment for sterile liquids, excipient properties driving dissolution, etc.) and then expand to end-to-end process. Companies can then leverage CPV trends that provide quick indications of less robust process areas.

So Much Data to Collect

Raw material attributes and process parameters, including lags between unit

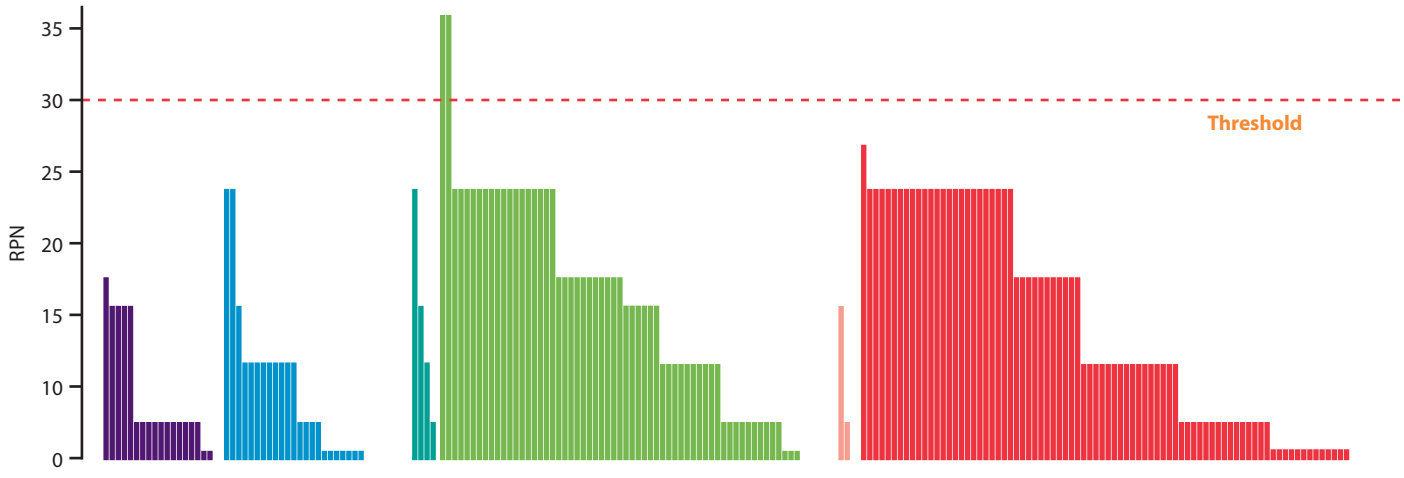


Figure 1 Risk Priority Number on Y-axis

operations and hold times, and in-process quality attributes need to be collected for as many batches as possible. Ideally, this information is collected directly from equipment and transferred, without human assistance/intervention, into databases for analysis. Often, this information is scattered and not suitable for analysis. In such cases, software tools can be developed to assemble available data from disparate sources and structure it for the purpose of analytics. This initial effort should contribute to, and be followed by, establishment of an infrastructure composed of databases and automated or semi-automated analyses to ensure data quality and integrity.

Statistical Analysis: A Numbers Game

Statistical analysis advances process understanding and knowledge. Results from statistical analysis help to separate signals from noise, differentiate causality and correlation, identify trends and make comparisons.

Methodologies applied to dataset assessment include, but are not limited to, data distribution, control charts, correlation analysis and multivariate data analysis (MVDA) tools such as partial least squares modeling and principal component analysis (PCA). Some of these methods, notably, control charts and capability calculations, are now routinely used, but more sophisticated techniques are needed to dissect a large amount of data to gain new insights, process knowledge and perform predictive behavior modeling.

MVDA can be used to show how raw material attributes impact CQAs and disrupt process performance, as not all raw material variability is neutralized by processing. Often, specifications for raw materials are set too wide to reflect the impact on final product quality attributes, causing true causality to be derived from statistical analysis of a large dataset. The example in **Figure 2** shows how attributes of dissolution rate controlling polymer significantly impact product assay and the data, colored by year of supply, show that raw material properties can be changed over time.

With this understanding, models can be constructed to predict CQA values for ranges of significant raw material attributes **(Figure 3).**

> **Pharma 4.0 requires analyzing process data in real time**

Modern pharmaceutical equipment includes sensors to collect a wide range of data to evaluate process dynamics. This is a bit of a double-edged sword as the increase in dimensions can complicate the analyses because many of the parameters, such as temperatures, measures of moisture and pressure, will be colinear and some of them will move in the same (or opposite) directions at the same time.

MVDA methods such as PCA or effect leverage plots are sophisticated methods that are made accessible to subject matter experts thanks to graphical and interactive software like JMP. These models identify primary control variables and changes in methods and materials that promise to reduce common cause variation. Low p-values (see the right-most column in **Figure 3)** indicate parameters that influence one or more outcomes. The p-values themselves are not always understood but, the horizontal bars to the left of that column convey the importance of each factor examined in the study. On the far left, the effect leverage plot, with points following the solid diagonal line, indicates that the model overall satisfies statistical assumptions. Good model fit alleviates the risk of overgeneralizing based on a few observations. Graphics allow subject matter experts to draw correct conclusions from the data.

Data analysis results should identify areas of product control strategy that need adjusting and show material attributes and process parameters are normal and variability is well controlled. End-to-end analysis should also provide additional insights into the overall process performance such as recommendations to perform periodic PCA on raw material attributes to detect shifts in a process. This cannot be seen in univariate trending. As a plus, improvements to the control strategy will provide direction for monitoring sensor placement for future automation.

After data from critical steps or the entire process have been analyzed, the team revises the CEM and FMEA with results from the MVDA study, including scientific knowledge used to interpret results. CEM with causality justification and FMEA with new scores capture knowledge gained and create a new baseline. The effectiveness of the results should also be evaluated periodically.

To maintain momentum, automating and repeating the analyses for other products as soon as possible is recommended. Companies can build a manufacturing information model for each technology platform to expedite results.

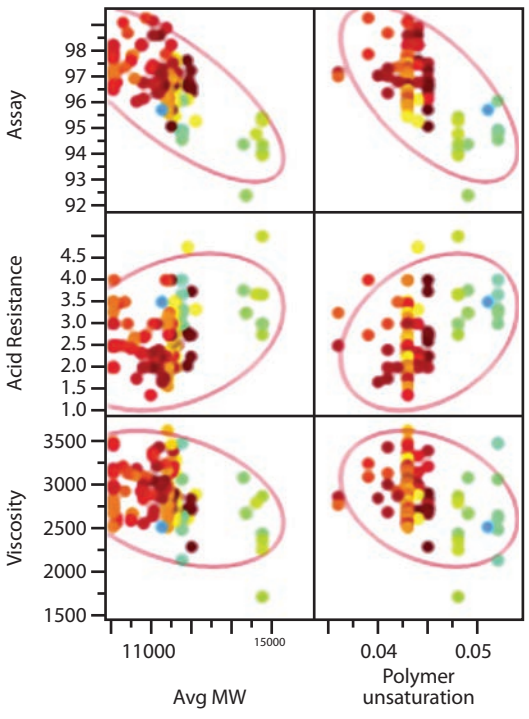


Figure 2 Change in Raw Material Properties Over Time

PHARMACEUTICAL | PERSONAL CARE

A DIFFERENT PERSPECTIVE ON **ANNEX 1.**

So, you've reviewed the proposed changes to Annex 1 in relation to your manufacturing processes, but...

...have you assessed the impact of likely changes relating to cleaning and disinfection procedures in your facility?

This is where Ecolab Life Sciences will help you ensure compliance, whilst optimising your processes.

Our highly experienced team can support you with solutions to the requirements that Annex 1 raises relating to your cleaning and disinfection.

The work you do impacts millions of lives, you need a reliable partner in life sciences to ensure compliance and patient safety.

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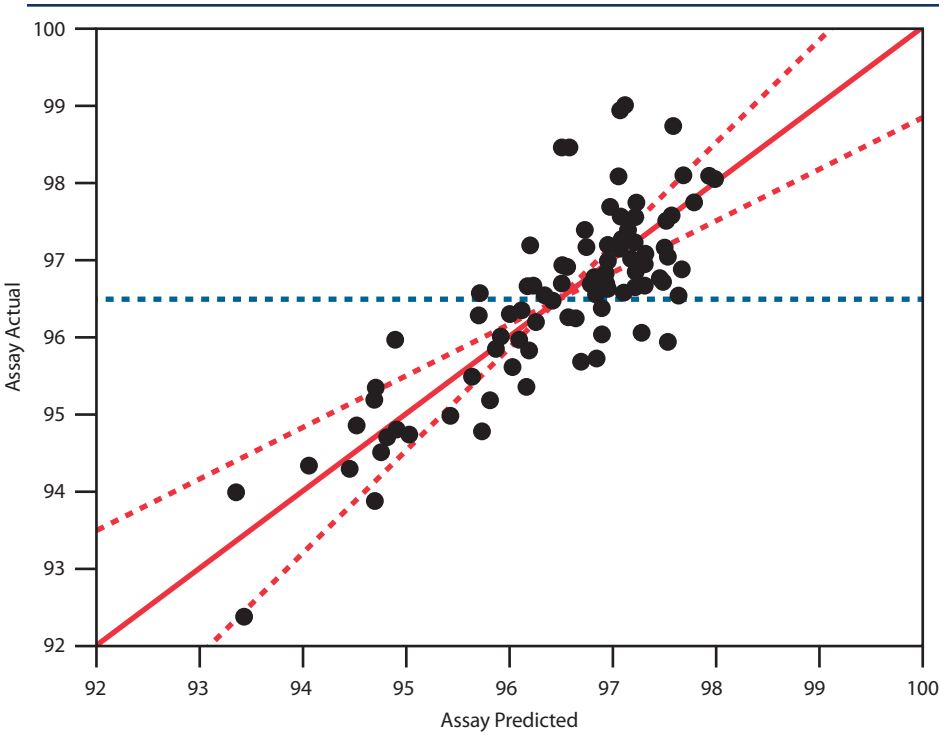

Figure 3 Prediction Model for CQA Values

The Transition to Pharma 4.0

Among the many challenges to adopting Pharma 4.0 is a need to house and process a rapidly growing volume of data (e.g., an online tablet inspection system generates up to 24 terabytes annually). Companies must be prepared to properly and efficiently analyze this data on a regular basis. Tools such as JMP, SAS and others allow subject matter experts to conduct advanced statistical analysis by way of visualization and interactivity.

Pharma 4.0 requires analyzing process data in real time or near-real time to allow staff to respond to signals and make decisions. Here, too, software will help but it is critical to avoid automating tampering, i.e., adjusting common cause variations, as this breeds process instability. Issues generally arise in the form of special-cause variation which will be the target for real-time analytical systems.

Real-time analytical activities characterize working in the system where operations are adjusted to best ensure quality. Analytical systems put in place to assist working in the system should also help in reducing common-cause variation. This means optimizing methods, materials, tooling and equipment. A design of experiments method provides the efficiency of simultaneously examining multiple factors in a brief period.

When organizations achieve a similar level of product and process knowledge for their entire portfolio, regardless of product time on the market, they are expected to find it easier to take advantage of new manufacturing technologies.

Beyond the need for the pharmaceutical industry to remain globally competitive (capacity, cost, agility) is increasing push by regulators for continuous product monitoring and process understanding ***(1).*** There is a growing expectation that manufacturers will perform such reviews much more frequently than annually. Pharma 4.0 technology allows for continuous, real-time monitoring of manufacturing processes, enabled by big data.

[Editor's Note: The online version includes additional figures and text along with an expanded version of **Figure 3.]**

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About the Authors

Jana Spes is a global pharmaceutical technical leader with experience in big and mid-size companies in US, Canada and Europe.

For almost three decades, **Wayne Levin** has worked with a variety of management, engineering and technical staff to improve their operations using applied statistical methods.

Big Data: The Panacea for Pharma's Ills?

Khan Lau, Promedica International

Two words are driving innovation within the pharmaceutical industry these days: "big data." Start-up companies like Datavant are receiving millions of dollars to harvest, organize, interpret and, hopefully, protect large amounts of data from a variety of stakeholders in the healthcare space ***(1).***

For example, the Open Medicine Institute, a digitally focused research clinic, serves as a free private repository for the collection of all patient information. This generates vast amounts of raw data that need to be curated—a situation also facing pharmaceutical development and manufacturing. For the pharma industry, this is an opportunity as well as a curse.

While the term "big data" has been around for a long time, an actual definition is elusive since its definition continues to fluctuate. In general, big data refers to extremely large datasets, both structured and unstructured, acquired daily by businesses. These large sets of data can be analyzed to reveal patterns or trends to gain insight into problems, provide support for decision-making and review performance objectively, often in real time. This data can also be actively measured so that outcomes and reporting can be adjusted as more information is obtained.

Now, with the broad use of electronic health records, unstructured data from diagnostic equipment and its own clinical trials, the pharmaceutical industry has a treasure trove of information from which to choose. By collecting these various datasets, pharma has an opportunity to gain novel insights that can enhance and accelerate the drug development process, especially in clinical trials ***(2)***, particularly as the manufacturing side explores the possibilities of big data ***(3).***

Big Data Meets Clinical Trials

Getting a drug product to market takes, on average, 10–12 years and requires hundreds of millions of dollars. Only one in one-thousand proposed new drug products completes this journey. Many potentially viable drugs are lost, abandoned or discarded, not necessarily due to efficacy or product safety, but because the high cost to survive a clinical trial cannot be justified. Some of these "lost" products include orphan indications, rare disease medicines and novel formulations. The loss of these products is due to a number of things—safety outcomes (phase I) effectiveness (phase II) and effectiveness plus adverse reactions (phase III) ***(4).***

Being able to predict how a compound might act would maximize positive outcomes, minimize errors and facilitate clinical trial enrollment. Big data could mitigate costs and shorten timelines for clinical trials, providing more justification for a drug's development.

Forecast with Predictive Modeling

Predictive modeling, or the ability to forecast the potential for a drug to be safe and effective for selective subsets of the population, is currently being used by a number of companies. When evaluating potential compounds with clinical data, predictive modeling could identify potentially successful molecules that would be both target-specific and safe and effective.

The use of big data to validate biomarkers in order to map treatment outcomes is a refined form of this type of modeling. In areas where the stakes of life and death are high, such as cancer treatments, this is especially true. A recent study used a Bayesian model to map cancer outcomes based on the genetic composition of the biomarkers found in "The Cancer Genome Atlas" database ***(5).*** By forecasting the potential success of the treatments, appropriate patient populations can be selected, therapies targeted, and dosages titrated to create a more patient-specific treatment.

Active Real-Time Monitoring

Currently, clinical trials are closely monitored with adverse events reported in a timely manner as dictated by best practice guidance. Data is reviewed for accuracy and a risk-based monitoring plan is created for each clinical study. Even with these precautions in place, however, there are still gaps in clinical trials due to the limitations in the ability of the monitor to provide 24-hour vigilance ***(6).*** Nowhere is this more apparent than in large global trials, where multiple time zones must be factored in. The opportunity to be alerted to safety or performance outcome signals could potentially allow for immediate

action on poor study-related processes or multiple adverse events where intervention might be needed.

Hidden Relationships Revealed

Big data can link comorbidities or associations with other diseases, as in the case of a study of U.S. military veterans that showed a correlation between periodontal disease and rheumatoid arthritis *(7)*. The U.S. Veterans Health Administration conducted a retrospective cohort study on 25 million patients to measure the relationship between periodontal disease and rheumatoid arthritis. The outcome indicated that patients who suffered from periodontal disease were 1.4 times more likely to have rheumatoid arthritis compared to other dental patients.

Post-Market Assessment and Safety

Big data modeling can also be used to review drugs that are currently on the market and look for new indications. By repurposing a pre-existing drug, a lower barrier to market entry is attained due to shorter approval time. In addition, using big data to review currently approved medications can be used to look for safety trends to prevent adverse events, off-label use or abuse.

Breaking Barriers to Big Data

While the advantages of applying big data in the current marketplace appear obvious, in reality, significant barriers still exist. Big data analytics are complicated and require a diverse set of skills for long-term support.

Identifying what to target can also be confusing, as there are many ways to implement big data. Devising a strategic plan requires both time and effort. Planning teams need to have fundamental research skills as well as statistical and analytical expertise. They will need a good understanding of both existing systems and the big data process.

“Big data analytics are complicated and require a diverse set of skills for long-term support”

Stakeholder positions can sometimes become entrenched. Those stances must be understood and addressed, and alternative arrangements or organizational restructuring must occur to prevent push back from stakeholders.

Cybersecurity remains high on the list of concerns, despite the fact that a good deal of data is encrypted. And U.S. and European medical privacy concerns must be considered.

Conclusion

While there are many advantages to using big data to improve outcomes or support clinical trials in drug development, there are a few pitfalls to consider.

Helping to uncover hidden relationships, maximize outcomes and minimize adverse events will expedite drug approval. As such, working with big data is certainly the future of the drug development process. And, if big data holds such major implications for drug development, how much more does it offer manufacturing?

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About the Author

Khan Lau is the Director of Clinical Operations for Promedica International, a niche CRO in the ophthalmology space.

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3] Train and Recruit for Industry 4.0

Not only will existing staff need to be trained on new technologies, but it is imperative to actively hire for individuals familiar with Industry 4.0.

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Role of Quality Culture on Operational Performance

Thomas Friedli, University of St.Gallen, Paul Buess, University of St.Gallen , Stephan Köhler, University of St.Gallen, Cylia Chen-Ooi, Amgen, Steven Mendivil, Amgen, and Denyse Baker, PDA

After many discussions within various facets of the pharmaceutical industry over the last three years, it became apparent that quality culture is increasingly considered a competitive advantage by operational excellence (OPEX) and quality executives. Recent research indicates the positive impact of quality culture on a broad range of performance indicators, especially on the success of quality improvement programs. Currently, however, a shared understanding of quality culture, as well as practical and accepted metrics for assessing quality culture, is lacking.

In 2014, PDA conducted a survey on quality culture in the pharmaceutical industry. Based on this data, quality culture was assessed in a later survey by distinguishing *quality system maturity* from *quality culture behavior* ***(1).*** The former focuses on objective characteristics of a quality system that can be verified upon inspection. In contrast, the latter aims to assess employee behavior at the site/organization associated with a strong quality culture, such as open communication and engagement. The later survey looked at whether there is a positive relationship between quality system maturity and quality culture behavior. If so, assessing the maturity of a quality system might serve as a surrogate indicator for quality culture behavior, which is comparably difficult to assess with reasonable effort. Statistical regression line analysis between composed quality system maturity and quality culture behavior scores revealed a positive correlation, thus supporting quality system maturity as a proxy of quality culture behavior.

Since 2016, the Institute of Technology Management at the University of St. Gallen, Switzerland, has been conducting a long-term research project on quality metrics, financed by the U.S. FDA. In the course of the project, the team integrated quality culture into the research scope. For operationalizing quality culture as a precondition for statistical analysis, the St. Gallen team adopted a two-sided perspective on quality culture ***(1).*** The quantitative research is based on the comprehensive St. Gallen OPEX database, consisting of more than 350 pharmaceutical production sites. The database consists of a broad range of performance metrics, along with so-called enablers, from several pharmaceutical companies worldwide.

The paper "The Impact of Quality Culture on Operational Performance – An Empirical Study from the Pharmaceutical Industry," available in the September/October *PDA Journal of Pharmaceutical Science and Technology,* summarizes the essential findings of this quality culture research. First, the research team retested the relationship between quality system maturity and quality culture behavior documented in 2015. This required the research team to operationalize both categories by matching the enabler from the OPEX database to the PDA definition. A regression analysis documents a strong positive correlation between both categories, substantiating prior findings. Second, the paper links the discussion of quality culture to performance outcomes. The team formulated the hypothesis that sites with a high capability of delivering high-quality drugs in the right amount and at the right time also demonstrate a significantly higher level of quality culture. A t-test analysis supports this assumption. Sites with high performance regarding quality and delivery reveal a significantly (p-value =.05) higher level of quality culture compared to sites with low performance.

The paper contributes to the ongoing discussion on quality culture. It confirms a positive correlation between improvements of the quality system maturity and the actual quality behavior of the employees. Further research might focus on identifying those elements of the quality system that have a comparably strong impact on quality behavior. In addition, the paper links quality culture, which is considered an enabler, to performance outcomes. The analysis indicates that investments in quality culture, including both the quality system and quality behavior, is positively associated with long-term benefits in terms of the ability to deliver high-quality products without the risk of shortages.

[Editor's Note: The PDA Education course, "Quality Culture Assessment Tool and Training – Taiwan," will be offered throughout November in Singapore, Taiwan and Santa Monica, Calif. For more information, visit www.pda.org/courses**.]**

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Hot Read: GMP in Practice

Rebecca Stauffer, PDA

In July, the fifth edition of the PDA/DHI book, GMP in Practice: Regulatory Expectations for the Pharmaceutical Industry *was published. The* PDA Letter *interviewed authors* ***Tim Sandle*** *and* ***James Vesper*** *about this bestselling book, which can be purchased in the PDA Bookstore (www.pda.org/bookstore).*

PDA Letter: Why do you think this book has consistently been a bestseller?

Sandle: There is nothing else out there that reviews the major GMPs in this way—breaking GMPs down into the most important areas, and then comparing the various clauses. This makes the book a must for those who are regularly inspected by more than one agency or wish to operate in different regions. Without this book, the task anyone must face in meeting these challenges is enormous.

Vesper: I suspect there are a couple of reasons. First, in many cases the GMPs are not all that specific—they give the "what" and sometimes a high-level "how." For example, U.S. GMPs, say "adequate space… to prevent mix-ups" (211.42(b)), but what does that really mean? By using different requirements from Canada, the European Union, WHO and ICH, we can get a richer understanding of what inspectors expect to see. Second, with globalization, we in the industry need to have a certain amount of harmonization to meet all applicable requirements. Companies have been doing that harmonization internally. This book is aimed at helping with that.

PDA Letter: What is different about this edition?

Sandle: The main difference is that all the GMPs have been updated. There have been some changes to U.S. GMPs due to new U.S. FDA guidances, a vast number of European GMP chapters have been rewritten and Canadian regulations have been completely revamped. In addition, the major regulatory agencies have adopted the ICH quality guidelines.

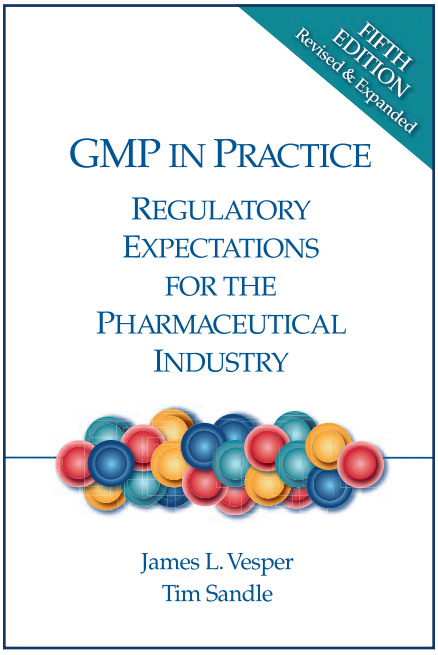
Putting all this together, it is clear that the scope of GMP continues to grow. This can be seen with GDP, which has become far more detailed in relation to the supply chain and with data integrity. Each major regulatory agency has issued guidance for the latter. A further change since the last edition has been the expansion in single-use, disposable technology, which brings with it areas to consider like leachables, extractables and methods of sterilization.

The book also highlights the potential applicability of Annex 1 to nonsterile manufacturing, and there are elements here that can be applied, such as personnel controls, disinfection and training.

Vesper: I suspect there are a couple of reasons. The EU GMPs have been updated since the 4th edition came out in 2011, so this new edition reflects these changes. We were all ready to send the manuscript to the printer when the Canadians finalized their revised GMPs that take effect in October of this year, so we went back and revised/updated those references. Because of the global concern for data quality and data integrity, we thought that deserved a dedicated chapter. Annex 1 was not finalized when we were writing this; we had to rely on the draft issued in December 2017. We looked at the draft requirements more from a conceptual standpoint.

PDA Letter: What are some of the common expectations that you have seen for elements included in a pharmaceutical quality system?

Sandle: The big push across the GMPs with pharmaceutical quality systems lies in the need for a holistic strategy, in that each of the various elements required for a robust quality system needs to be joined together into a coherent whole. Structuring an internal company document around the different chapters in this book would provide a useful framework for companies that lack such a document. This is also important because a company's pharmaceutical quality system will be evaluated during an inspection, and it plays an important role in the new drug product submission process.



Vesper: Some of the "themes" or common threads that I see running through the pharmaceutical quality system include not just risk management but risk-based thinking. To me, this means not just doing formal risk assessments but viewing all that we do in terms of understanding risks and taking appropriate actions to reduce those risks that we know to be significant. Also, looking at trends—what are the data telling us and how should we respond? Management support is a third theme—understanding what the issues really are and taking proactive steps to resolve them.

PDA Letter: Does this book address new technologies and processes, such as parametric release?

Sandle: The book contains all of the guidance on parametric release, which is linked to the chapter on terminal sterilization. We recognize that parametric release is of interest to a number of firms, in terms of saving time on batch releases and with resources. There are other benefits as well, like manufacturing flexibility (moving product to market more rapidly where ➤

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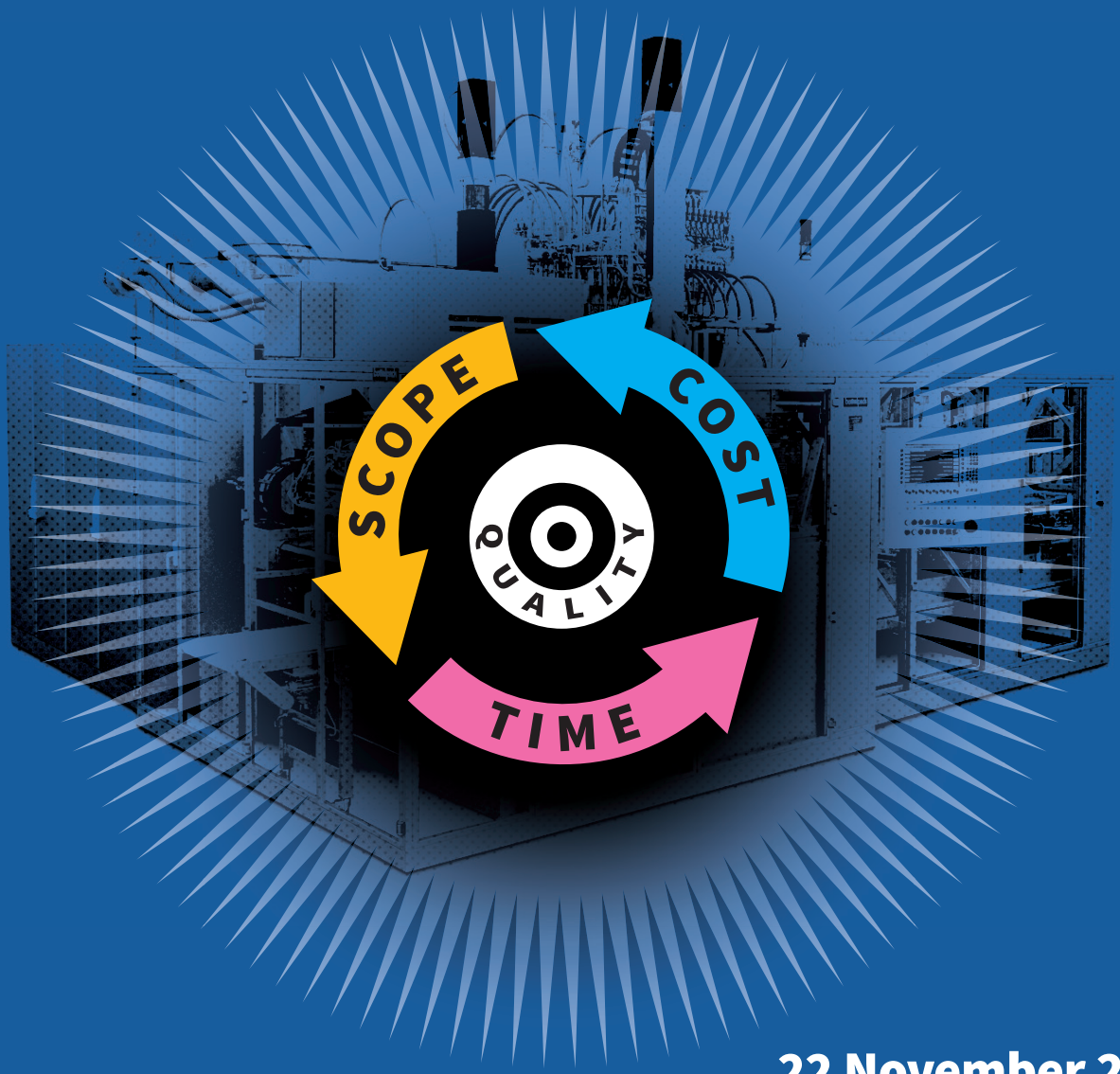

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there are drug shortages), gaining better process understanding and strengthening manufacturing controls.

Parametric release also features in the parts of the book applicable to nonsterile manufacturing, such as the use of scientifically sound in-process controls and chemical measurements.

PDA Letter: Who would be best served by reading this book?

Sandle: The audience is anyone involved with pharmaceuticals and healthcare products, for there is no area untouched by GMP—from purchasing to distribution of medicines. The substantive sections of the book, which are about manufacturing, laboratory testing and release, will appeal to quality assurance, quality control, validation, manufacturing and inspection departments. This enables companies to benchmark their practices.

The book is also useful when preparing for international inspections, especially if the company is unfamiliar with the regulators who will be conducting the audit. So, those in the United States who are unfamiliar with inspectorates following EMA GMPs can get a feel for what is required and, likewise, will those in Europe can better prepare for a U.S. FDA inspection.

Vesper: From what people have told us about previous editions, it has been used as a reference by those in quality assurance and also technical/manufacturing operations. One quality assurance person said it was valuable to have expectations covering a certain topic pulled together in one reference. Another firm used it to train supervisors, asking them how GMP expectations were realized in their operations and what needed to be improved.

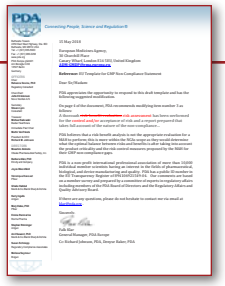
It will also help readers have much more fascinating conversations at dinner parties.

About the Experts

Tim Sandle, PhD, is a pharmaceutical microbiologist with 25 years of experience working in the pharmaceutical and healthcare sectors.

James Vesper, PhD, has worked in the pharma/biopharma industry for more than 35 years, starting out at Eli Lilly and Company where his last role was leading the GMP Training and Education group.

Risk-Benefit Analysis More of NCA Scope



15 May 2018

European Medicines Agency
30 Churchill Place
Canary Wharf, London E14 5EU, United Kingdom
ADM-GMDP@ema.europa.eu

Reference: EU Template for GMP Non-Compliance Statement

Dear Sir/Madam:

PDA appreciates the opportunity to respond to this draft template and has the following suggested modification.

On page 4 of the document, PDA recommends modifying item number 3 as follows:

A thorough risk-benefit evaluation risk assessment has been performed for the control and/or acceptance of risk and a report prepared that takes full account of the nature of the non-compliance…

PDA believes that a ~~risk-benefit analysis~~ is not the appropriate evaluation for an MAH to perform; this is more within the NCA's scope as they would determine what the optimal balance between risks and benefits is after taking into account the product criticality and the risk control measures proposed by the MAH for their GMP non-compliance gaps.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. PDA has a public ID number in the EU Transparency Register of 894106921549-04. Our comments are based on a member survey and prepared by a committee of experts in regulatory affairs including members of the PDA Board of Directors and the Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me via email at klar@pda.org.

Sincerely,
Falk Klar
General Manager, PDA Europe
Cc: Richard Johnson, PDA, Denyse Baker, PDA

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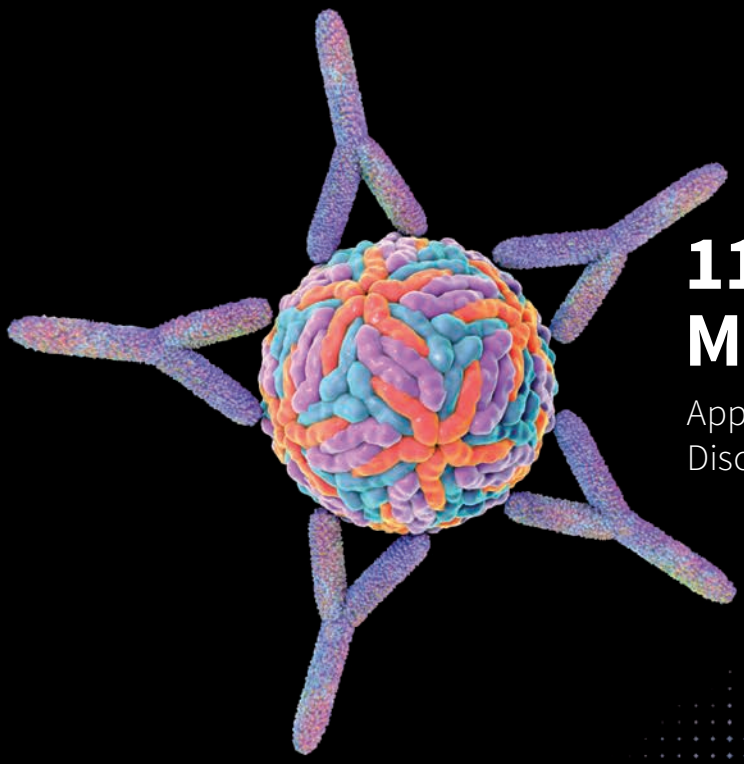

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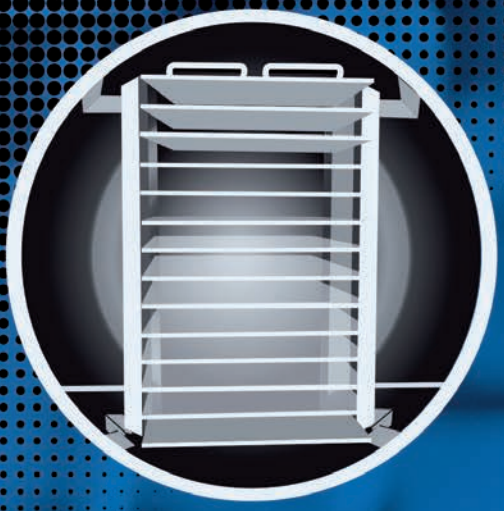

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Russian GMP Inspections: Part I

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

Over the past two years, many international companies have hosted Russian inspectors at their manufacturing sites ***(1).*** Below is information describing the general regulatory landscape in Russia, history of the Russian GMP inspectorate and common observations made by Russian inspectors. This can help companies prepare for Russian inspections, anticipate the types of findings that may be delivered and understand how to address these findings.

General Regulatory Landscape

There are four regulatory bodies concerned with the field of manufacturing, control and distribution of medicine in Russia: The Ministry of Health (MoH), the Ministry of Industry and Trade (MoIT), the Federal Service for Surveillance in Healthcare (Roszdravnadzor), and the Federal Service for Veterinary and Phytosanitary Surveillance (Rosselkhoznadzor). The responsibilities for each are outlined below.

MoH:

- Registration of drugs
- Control of clinical trials
- Expert evaluation of drugs (Federal National State-financed Institution "Scientific Center for Expert Evaluation of Medicinal Products" of the Russian Ministry of Health)
- Issuing of marketing authorizations
- Maintenance of registry for medicinal products

MoIT:

- Licensing of drug manufacturers and maintaining the register of licenses
- Licensing control
- GMP inspections of Russian drug manufacturers
- GMP inspections of foreign drug manufacturers (Federal State Institute of Drugs and Good Practices ("SID and GP") of the Russian Ministry of Industry and Trade)

Roszdravnadzor:

- Field surveillance of medicinal products and medical devices circulation
- State control over the quality and safety of medical activities
- GDP inspections
- Pharmacovigilance

Rosselkhoznadzor:

- Registration of veterinary drugs
- State supervision in the field of veterinary drugs circulation
- Licensing of veterinary drug manufacturers and maintaining the registry of licenses
- Licensing supervision
- GMP inspections of Russian veterinary drug manufacturers
- GMP inspections of foreign veterinary drug manufacturers

In addition, in-country certification is required in Russia ***(2).***

Establishment of the Russian GMP Inspectorate

The establishment of the Russian GMP inspectorate is directly connected with introducing GMP rules in Russia. The very first version of Russian GMP guidelines, *Rules of Organization of Drug Manufacture and Quality Control,* were drafted and enacted in 1991. While these became effective regional and national standards, they still had fundamental differences from accepted EU GMP.

Then, in 1998, the Russian industry standard, *Rules of Organization of Drug Manufacture and Quality Control (GMP),* was approved. This standard embraced the principles of EU GMPs to the greatest extent possible. It became effective July 1, 2000, covering all manufacturing facilities, regardless of their legal status or form of ownership. Under this standard, when registering a newly built or reconstructed facility or importing drug products into the Russian Federation, a manufacturer must provide a GMP certificate for the manufacturing site issued by the manufacturer's inspectorate.

Today, the following documents regulate the manufacturing of medicines:

1. Federal law No. 61-FZ dated April 12, 2010, "On Circulation of Medicines"

2. Federal law No. 99-FZ dated May 4, 2011, "On Licensing of Certain Types of Activity"

3. RF Government Decree No. 1314 dated Dec. 3, 2015, "On Determination of Compliance of Medicinal Product Manufacturers with the Requirements of the Good Manufacturing Practice" (together with "Rules for Organization of Inspections of Drug Manufacturers for Compliance with Good Manufacturing Practice and Issuance of GMP Certificates")

4. Order No. 916 dated June 14, 2013, "On Approval of Good Manufacturing Practice Standards for Medicinal Products"

5. Order No. 1997 dated Dec. 12, 2013, "On Approval of Recommendations for Organization of Manufacture and Quality Control of Medicinal Products"

Currently, two different groups of inspectors are responsible for the inspection of local Russian and foreign manufacturers. The MoIT's Department of Pharmaceutical and Medical Industry Development Section of Drug Manufacture Licensing and Inspections is charged with the licensing of Russian manufacturers, including GMP inspections. Additionally, the MoIT makes decisions on issuing GMP certificates to both Russian and foreign manufacturers. In 2017, there were 13 inspectors in this subdivision.

The State Institute of Drugs and Good Practices (SID and GP), which began in 2016, conducts inspections of foreign pharmaceutical manufacturers ***(3).*** These inspectors must meet the following requirements: hold a graduate degree in science or pharmacy, have more than five years of work experience in manufacturing or quality assurance and have knowledge of a foreign language. ➤

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The first group of inspectors underwent specialized training, conducted by experienced inspectors, that consisted of three modules: classroom review, observation of an inspection conducted by one of the trainers and, then, conducting their own independent inspection under a trainer's supervision. After the training, the newly minted inspectors were awarded specialized diplomas and received international WHO certificates to support their capacity to act as inspectors. As of 2017, SID and GP included 58 inspectors.

Since then, between Dec. 18, 2015 and April 23, 2018, 896 foreign manufacturing sites have been inspected by Russian inspectors; 684 certificates have been issued and 196 have been denied. As the Russian GMP inspectorate has become better established, more than 9,000 deficiencies have been identified, including 2,500 critical violations, 3,203 major deficiencies and 3,375 minor deficiencies.

How to Prepare for Russian Inspections

Preparation for an inspection is crucial and should be initiated long before the Russian inspectors arrive at the manufacturing site. For the first step, the manufacturer's office in Russia submits a set of documents to MoIT that include:

1. GMP application form administration document with manufacturing site details (name, address, contact info), Qualified Person (QP) details (name, position, email, phone, fax—which should be identical to the actual site master file) and manufacturing license details (site number, date, agency contact details)
2. Power of Attorney
3. Site Master File
4. List of complaints within the last two years
5. Product list per manufacturing site
6. Manufacturing license (notarized translation)
7. Letter of agreement for inspection (signed by site)
8. Fee payment confirmation

To prepare for an inspection, the host site needs to complete a Form 3, which describes all products and manufacturing steps at the site. The manufacturing site needs to cooperate fully with the company's Russian office. If possible, representatives of the Russian office should visit the site before the inspection to become familiar with all the manufacturing steps. If the form is not filled out correctly, inspectors may have additional questions and observations, which has happened in some cases.

Translation is the next critical step. Knowledge of the Russian language is not enough—an interpreter must be a certified translator and familiar with technical terminology. Before the inspection, interpreters must be aware of Russian GMPs. They should also visit the site before the inspection to prevent any potential mis- ➤

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understandings or inaccurate translation that could result in observations.

Additionally, host site personnel should receive cultural training that explains Russian communication styles and includes a brief presentation on Russian history and culture. Site personnel need to be able to describe the supply chain cycle for a product once it has left the site and is released to the Russian market. Russian inspectors take into account the manufacturing site, in the context of product supply to the Russian market according to the requirements of Normative Documentation (ND); it is crucial for site personnel to understand this perspective when preparing for the inspection. Very often, employees at each site are only aware of their specific tasks due to the decentralized nature of modern manufacturing.

Once an applicant submits the full set of documents, members of the inspection team are assigned within five business days. A lead inspector on this team coordinates the inspection from planning to CAPA evaluation.

The inspection should take no more than ten days. An inspection plan is drafted with a list of documents to be prepared for the inspection. This occurs approximately two weeks before the inspection.

The fee for the onsite inspection is calculated according to a formula approved by the Russian government. This formula is based on the complexity of the production process and the variety of product types to be inspected.

During an inspection of a foreign manufacturing site, findings may be classified into three general categories:

1. Noncompliance with the requirements of the registration dossier approved in the Russian Federation

- One frequent observation is that finished product released by the QP does not comply with the ND. This often occurs when regulatory affairs personnel are not located at the site. Additionally, it is possible that upon initial submission, regulatory files were reflective of the actual manufacturing and testing procedures at that time. Changes in process or methods may not have been reported to MoH, however, and may not be reflected in the Russian dossier.
- Discrepancies between the actual manufacturing and testing practices and the approved regulatory dossier is obviously a breach of GMP requirements. Russian inspections that reveal such deficiencies will result in corrections and amendments to regulatory documents in line with actual processes.

2. General GMP deficiencies related to documentation, personnel training, process, analytical methods, rooms, equipment validation/qualification, etc., including:

- Noncompliance with Annex 1 requirements, for example, no continuous monitoring at the most critical points, and insufficient process validation
- Absence of dedicated isolated areas for storage of rejected/recalled products, as well as of rejected starting materials and excipients (including cases with fully computerized storage systems)
- Maximal allowable carry-over (MAC) calculations for cleaning validation studies not based on toxicological studies
- Absence of traceability of the quantity of printed packaging materials with applied variable data during production
- Absence of verification (i.e., validation) of time intervals between the end of the production process and equipment cleaning, as well as between the executed cleaning and the start of the next process (dirty hold time/clean hold time)

3. Observations related to noncompliance of foreign sites with Russian-specific compendial or other regulatory requirements, particularly the following monographs:

- **OFS.1.2.4.0004.15 Abnormal Toxicity.** The requirement to carry out this test is usually listed in Russian NDs for sterile drugs as requested by the Federal National State-financed Institution Scientific Center for Expert Evaluation of Medicinal Products. This test is not performed in Europe or the United States, as animal tests are prohibited there, and absence of abnormal toxicity is proved by other methods ***(4).***
- **OFS.1.1.0009.15 Shelf Life of Medicinal Products.** This pharmacopeial monograph requires a sterility test to be performed at the end of the shelf life. At the same time, many foreign manufacturers perform a sterility test upon product release only and have substituted this test at the end of shelf life with a container closure integrity test ***(5).***
- **OFS.1.2.4.0002.15 Microbial Purity.** Interpretation of this monograph can trigger some major and critical observations based on the requirement for sterility of drug substance used for the manufacture of sterile drugs, as well as the requirement for analysis of microbial purity for each batch of nonsterile drugs.

[Editor's Note: This article continues on the *PDA Letter* website**.** It is also the first in a two-part series. Part II will appear in the Nov/Dec issue and can also be found on the Letter website**.]**

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One Quality Voice

PDA Task Force Unites Quality Leaders for Positive Change

Melissa Seymour, Biogen

In 2016, PDA established the Post-Approval Change: Innovation for Availability of Medicines (PAC iAM[SM]) task force. The focus of this task force has been to drive dialogue between industry and regulators to transform the current paradigm for post-approval changes (PACs). Early on, the task force identified an effective pharmaceutical quality system as a prerequisite for innovation through PACs as part of lifecycle management. This resulted in the document, "PDA Points to Consider: Technical Product Lifecycle Management, Pharmaceutical Quality System Effectiveness for Managing Post-Approval Changes."

This task force is also planning to deliver a technical report titled *Post-Approval Change Management and Implementation for Biologics and Pharmaceutical Drug Products – A User's Guide*. This technical report is intended to provide the reader with practical solutions aligned with ICH Q12: *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* concepts, including specific examples and tools. A prime focus within this technical report involves relying on a company's internal pharmaceutical quality system as a bedrock for managing change.

In late August, the task force assembled senior industry quality leaders at PDA's headquarters in Bethesda, Md., to collaborate on how the industry can drive continuous improvement in the management of PACs by leveraging the pharmaceutical quality system. Twenty heads of quality, representing the branded, generic, biotech and contract manufacturing sides of industry were in attendance. A notable outcome of this workshop was a commitment from the quality leaders to create "One Quality Voice" on the importance of implementing new knowledge to continually improve in order to meet the objective of reliably producing high quality products for patients, per CDER's **Janet Woodcock.** This was an energetic and passionate discussion that led to some practical actions for industry to take including:

- Standardizing the approach for management of PACs
- Developing standardized risk-based approaches to PACs to allow timely implementation of new knowledge via an effective pharmaceutical quality system
- Raising awareness of the global complexities associated with PACs
- Defining metrics capable of distinguishing an effective pharmaceutical quality system

The senior quality leaders will continue to meet and drive progress on tangible solutions for managing PACs in the pharmaceutical quality system. The PAC iAM[SM] task force welcomes participation from other heads of quality who did not attend this meeting.

The complexity of global regulatory PAC/variation processes is a challenge for the industry, and the PAC iAM[SM] task force is another example of PDA's commitment to advancing continuous improvement and facilitating dialogue to benefit the patients we serve. More information regarding the task force can be found at www.pda.org/conference/pac-iam/home.

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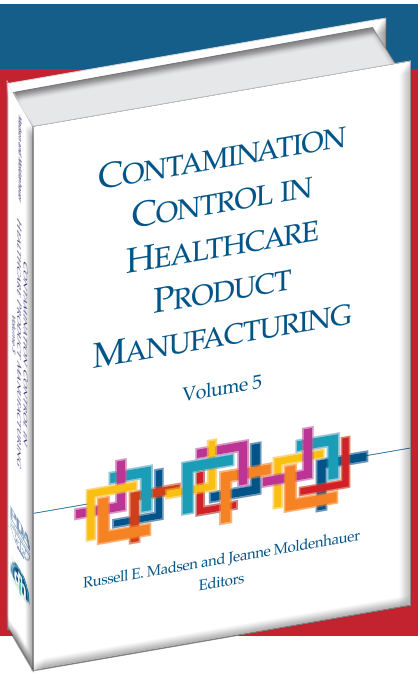

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