People • Science • Regulation

PDA Letter

Volume LII • Issue 9 www.pda.org/pdaletter October 2016

The Role of a Person in Plant for Early Development Projects 22

Follow the icon to find articles on the ***2016 PDA Outsourcing/CMO Conference***

Calling All Active PDA Members – Vote Now!

Online voting is now open for the 2017 PDA Board of Directors Election

PDA members, online voting has opened for the **2017 PDA Board of Directors Election**. Take a moment and vote for your candidates of choice at **pda.org/vote**.

All PDA members in good standing as of **midnight on August 25, 2016 are eligible to vote**. Voting closes at **11:59 p.m. EST on November 16, 2016**. Any votes cast after this date and time will not be accepted.

If you need assistance, please contact PDA at +1 (301) 656-5900 or vote@pda.org.

Thank you for being a valued PDA member and for voting.

Instructions for Voting:

- Go to **pda.org/vote**
- Log into the system using your PDA Member number and last name
- Please read the instructions for each question carefully
- Review the choices for each position then select a candidate for that position
- When you complete your ballot, review your selection and then check the participant consent box and click on the "SUBMIT" button
- You have now completed the voting process
- You can view and print your receipt or just exit the PDA eBallot System

pda.org/vote

The Parenteral Drug Association presents the...

2017 PDA Annual Meeting

Innovation in Manufacturing Science and Technology

April 3-5, 2017 | Anaheim, California

Anaheim Marriott

Exhibition: April 3-4 | Post-Meeting Workshop: April 5-6 | Courses: April 6-7

#2017Annual

Register before January 20 and save up to $600

Conference Theme: *Manufacturing Innovation: The Next Wave of Sterile and Biopharmaceutical Science, Technologies and Processing*

Join us in Anaheim, CA for the PDA Annual Meeting to gain best practices and learn how industry is applying novel approaches for development and commercialization of pharmaceutical and biopharmaceutical products.

The *2017 PDA Annual Meeting* will focus on advanced therapeutic strategies, including immunotherapy and gene- and cell-based therapies and delivering them to patients.

Explore current and future trends in process development and manufacturing, including:

- Next generation processing and facilities
- Application of big data for process design and optimization
- Accelerating the industry response to healthcare needs

Take advantage of networking opportunities and see the latest technology in action in the Exhibit Hall.

Be a part of this exciting meeting filled with novel approaches and strategies for bringing products to market!

Learn more and register at pda.org/2017Annual.

PDA Letter

Volume LII • Issue 9 www.pda.org/pdaletter

Cover

Trust is important in any relationship, particulary the relationship between a sponsor company and a contract manufacturing organization (CMO). As outsourcing becomes more and more important in the strategic supply chain in the biopharmaceutical industry today, the effective management of the contract manufacture organizations (CMOs) is a topic of high interest. Many of the pioneers from both the customer and CMO sides gathered at the PDA Outsourcing/Contract Manufacturing conference in 2014 to discuss "Is outsourcing your weakest link?"

Cover Art by Wavebreakmedia | iStock Photo

Departments

Contents

Features

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.

PDA Task Force Releases Post-Approval Changes Workplan

PDA's Post Approval Change Innovation for Access to Medicines (PAC iAM[sm]) Task Force of volunteer industry experts has issued a call to action (see story on p. 34), inviting the broader pharmaceutical industry and regulatory community to join with them in tackling this "wicked problem" (see http://alturl.com/djqrc).

Current disharmonized national and regional post-approval change (PAC) regulations require companies to submit filings with agencies worldwide in order to gain permission to make most changes to manufacturing systems, analytical methods, and processes. In many cases, the PAC process takes several years, and manufacturers must produce multiple batches of the same product while they await approval for a change in one region/country, which has already been approved in others.

PDA's task force has the following objectives:

- **Bring awareness** to current challenges and enable stronger collaboration amongst opinion leaders and key stakeholders (within industry, regulatory agencies, and other relevant stakeholder forums).
- **Foster a science and risk-based approach** to PAC management and regulatory decision making for global product quality, safety, and efficacy assessments
- **Encourage international convergence/standardization** in PAC management in a manner that can foster and **enable mutual reliance** between regulatory authorities
- **Manage PACs through** the use of **an effective Product Quality Systems (PQS)**

The task force will produce several position papers for the *PDA Journal of Pharmaceutical Science and Technology* over the coming months. The group will also be conducting an industry survey to gather information to support a future PDA technical report and examples of global PAC protocols on the topic.

PDA IS PLEASED TO INTRODUCE THE

Refer a Friend Program

Get rewarded for referring PDA – Give $10, Get $10!

HOW IT WORKS:

PDA wants to say thank you to its loyal members who refer their friends and colleagues.

When you refer a friend or colleague to join PDA, that person will receive $10 off the PDA Individual Membership fee.

And, as a thank you for the referral, you will receive a $10 Visa gift card when that person joins. There is no limit – the more people you refer, the more you benefit.

It's a win for everyone!

Visit www.pda.org/refer and start to "Give $10 and Get $10" today!

Watch PDA Chair Discuss Supply Chain Issues

In the latest *PDA Letter* "On the Issue" video, PDA Chair **Martin VanTrieste,** recently retired from Amgen, discusses the issues currently impacting the pharmaceutical supply chain, including new serialization requirements from the EU and the continued threat from counterfeit pharmaceuticals. He draws from his years of experience to discuss what industry can do to respond to these supply chain challenges.

To access the video, visit https://www.pda.org/pda-letter-portal/multimedia/videos.

Don't Forget to Vote!

All PDA members in good standing are eligible to vote for candidates for the 2017 Board of Directors. The election closes at 11:59 p.m. EST on Nov. 16. Members can vote online at www.pda.org/vote or at conferences in the U.S. and Europe prior to the closing date.

Information about the candidates can be found at www.pda.org/election. Up to four board members may be selected.

PDA Volunteer Spotlight

Adalberto Ramirez

- Vice President of Corporate Quality
- *Amgen*
- Member Since | 2007
- Current City | San Juan, Puerto Rico
- Originally From | Morovis, Puerto Rico

PDA also offers a great resource to expand your network

What is your most memorable experience at PDA to date?

I had the honor of leading the 2014 *Universe of Pre-filled Syringes and Injection Devices* Program Planning Committee and it was a major success. More than a thousand people attended the conference—way beyond all expectations! The Committee was very happy with the excellent results, and there was a major sense of achievement as a team.

It was overall a great experience. Many dedicated professionals came together to volunteer for a common objective: the success of the conference. Ultimately, it was a real team effort; everybody did their part and everyone delivered on their individual commitments.

What advice would you give to members interested in becoming a chapter leader?

First, be active in all PDA sponsored activities. Then, invite other industry colleagues and friends to participate. Next, volunteer on groups responsible for technical discussions and papers. Finally, as you work your way up, volunteer for the different roles required for various PDA sponsored activities.

How has PDA contributed to your professional career?

PDA has provided a forum for technical discussions. This enables a proper setting for discussing the issues affecting the industry and stimulating analysis of current regulatory trends. PDA also offers a great resource to expand your network, get to know the suppliers, and learn about new technologies/solutions available to help you.

Okay, so I've just joined PDA. What do I do next?

Get involved! Participate. Volunteer for work. Be an active member. Make the difference!

What's something not many know about you?

I am a frustrated athlete. While I play many sports (golf, tennis, basketball, volleyball, among others), I'm not that good at them. But I still have fun playing them!

The Parenteral Drug Association presents the...

2016 PDA Data Integrity Workshop

1946 70TH ANNIVERSARY 2016

PDA Parenteral Drug Association

November 8-9 I Berlin, Germany
December 7-8 I San Diego, CA

The **2016 PDA Data Integrity Workshops** will include a blend of presentations from regulatory and industry experts, case studies and round table discussions. Special focus on exploring the multiple facets of data integrity, such as quality culture, human behavior, training needs, and technology requirements, will help attendees get a broad perspective on common factors, and cause and effect. Through round table discussions, attendees will learn about best practices for preventing, detecting, mitigating and remediating data integrity issues. Ample opportunity will be provided for attendees to network with industry peers, regulators and solution providers to enhance the overall learning experience.

8-9 November 2016

Titanic Chaussee Hotel
Berlin | Germany

europe.pda.org / 2016data
#2016data

chapter update

日本PDA製薬学会がデータ・インテグリティのシンポジウムを開催

ERES委員会委員長、テバ製薬株式会社 合津 文雄

日本PDA製薬学会の電子記録・電子署名(ERES)委員会は、データ・インテグリティに関するシンポジウムを6月14日に東京で開催しました。160人を越える参加者を得て、技術的および規制環境において変化してきたデータ・インテグリティの役割について学びました。

最初の講演では、ERES委員会の新井洋介さんと荻原 健一さんが、規制の背景と解決策について講演し、それを受けて David Stokes さんは、データ・インテグリティのライフサイクルにおける、リスク低減について非常に広範な講演を行いました。続いて、ERES委員会の村上大吉郎さんが「GDP (Good Distribution Practice) 管理に求められるIT」と題した講演において、データ・インテグリティを実現する実用的な取り組みを紹介しました。最後に講演したJames Akersさんは、GMP規制の発展過程におけるデータ・インテグリティの重要性について歴史的な視点から語りました。

これらの興味深い講演に続いて、講演者等によるパネル・ディスカッションを行いました。パネリストは全員、データ・インテグリティを支えるのは「トップから」であることに賛同しました。すなわち、上級管理職は、データ改ざんから生じる悪意をもった犯罪的行為が起こる可能性を最小化する統合的組織的環境を構築し、支援しなければなりません。こうした環境において上級管理職は、会社がデータ・インテグリティのガイドラインを順守し、その品質システムの継続的改善が維持されることを確実なものとする必要があります。

The Japan Chapter exhibited at the inaugural PDA Europe *Annual Meeting* this June in Berlin

それに加えて、企業のクオリティ・カルチャーは、自身の作業手順上のミスや、GMP不適合について報告することを奨励しなければなりません。電子的なデータ入力と保存は今日の産業界で広く普及し、製品のライフサイクルは複雑になっているため、データ・インテグリティは規制適合性に明確に焦点を当てる必要があります。企業の上級管理職は、データ・インテグリティをもたらすプロセスやITシステムを設計し、すべてのデータが入力され、タイムリーに正確性を確認しなければなりません。

日本PDA製薬学会は、シンポジウムの成功に尽力いただいた、ERES 委員会メンバーと **David Stokes** さん、**James Akers** さんに感謝します。

所属等

James Akers, PhD, President, Akers Kennedy and Associates, Inc./Shibuya Corporation

新井洋介, 株式会社シグマクシス

村上大吉郎, 特別顧問, 平原エンジニアリングサービス株式会社

荻原 健一, 代表取締役, 株式会社シー・キャスト

David Stokes, Director and Principal Consultant, Convalido Consulting Limited UK

Japan Chapter Holds Data Integrity Symposium

Fumio Gotsu, Teva Pharma Japan Inc., PDA Japan Chapter ERES Committee Chair

On June 14, the PDA Japan Chapter Electronic Records and Electronic Signatures (ERES) Committee hosted a symposium on data integrity in Tokyo. More than 160 attended this event to learn more about the role of data integrity in a changing technological and regulatory environment.

Yosuke Arai and **Ken-ichi Ogihara,** both ERES Committee members, delivered the first presentations, providing a background on key regulatory issues as well as potential solutions. Following these talks, **David Stokes,** delivered a very comprehensive presentation on risk mitigation within the data integrity lifecycle. Then, another ERES Committee member, **Daikichiro Murakami,** gave extensive information on practical data integrity solutions in his talk, "IT Required for GDP (Good Distribution Practice) Management." And finally, **James Akers,** PhD, gave a historical perspective on the importance of data integrity in the evolution of GMP regulations.

Following these fascinating presentations, the presenters participated in a panel discussion.

The PDA Japan Chapter acknowledges the efforts of all the ERES Committee members as well as David Stokes and James Akers in support of this very successful symposium.

[Editor's Note: Read more about the panel discussion online at www.pda.org/pda-letter-portal/archives/full-article/japan-chapter-holds-data-integrity-symposium.]

PDA Who's Who

James Akers, PhD, President, Akers Kennedy and Associates, Inc./Shibuya Corporation

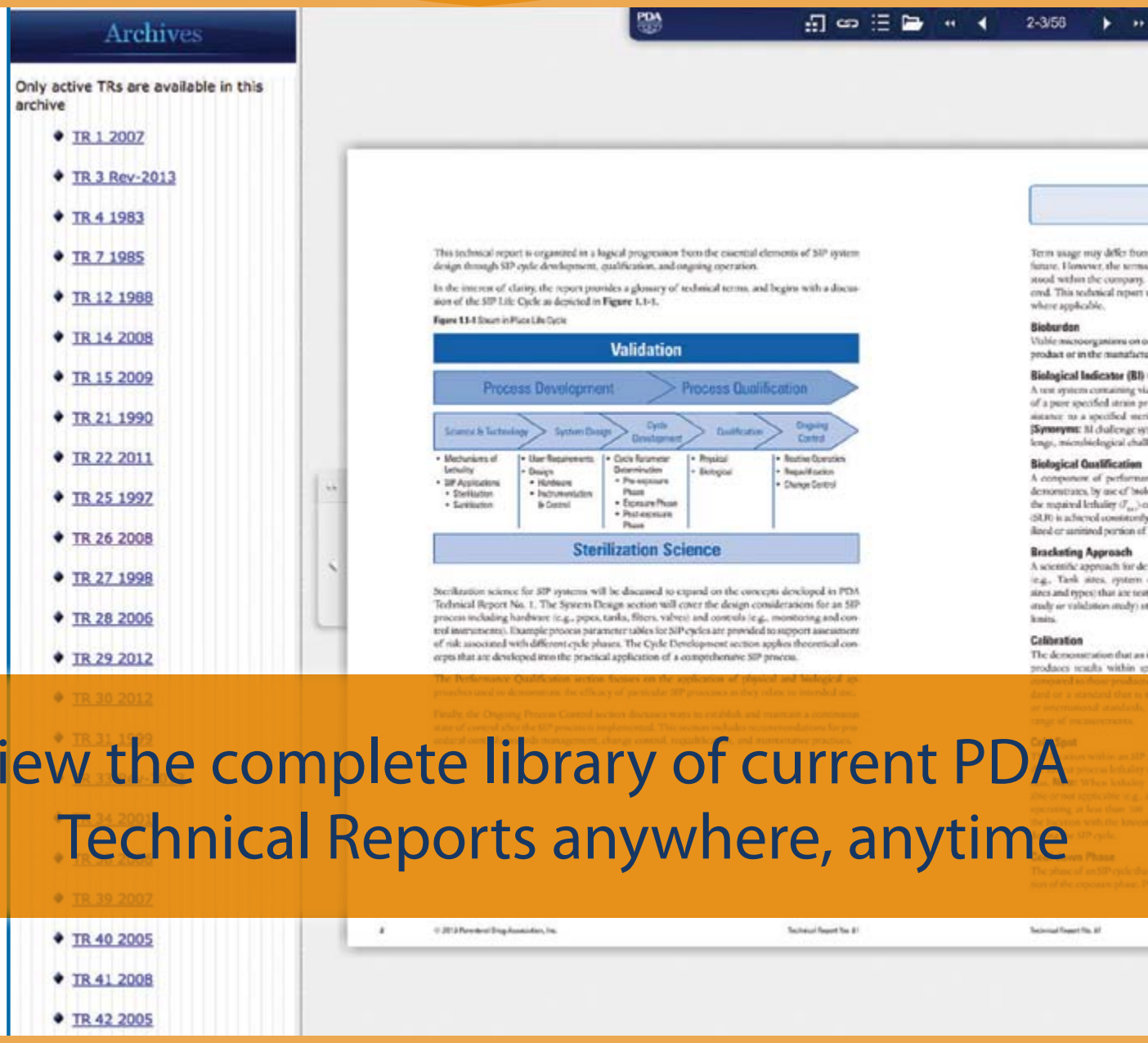
Yosuke Arai, SIGMAXYZ Inc.

Daikichiro Murakami, Special Adviser, Hirabara Engineering Service Ltd.

Ken-ichi Ogihara, CEO, C-Cast Co

David Stokes, Director and Principal Consultant, Convalido Consulting Limited UK

PDA's Technical Report Portal



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

For more information and to view PDA's Technical Report Portal please visit:

trarchive.pda.org/t/26426

Licensing options available; contact Janny Chua at chua@pda.org

tales from the trail

When a Routine Trip Becomes a 1980s Comedy of Errors

Walter Morris, PDA

Business trips can be mundane, but every once in a while they turn into an unexpected adventure of the kind depicted in the 1987 **Steve Martin/John Candy** comedy *Planes, Trains and Automobiles*. My trip to Berlin for the inaugural PDA Europe *Annual Meeting* in June was just such a trip!

Flying from Washington, D.C. to Berlin should be uneventful, but this time I chose the uncommon route through Reykjavik, Iceland on the even more uncommon carrier WOW Airlines. "Not advisable," warned PDA's **Rich Levy,** but I needed to be economical because I was taking my son, **Ryan,** as a high-school graduation gift.

Cost savings in hand, Ryan and I arrived at BWI airport on a nice Saturday evening only to learn our flight to Reykjavik was delayed by two hours. As we ate dinner in the concourse restaurant, I worried about the possibility of missing our connecting flight to Berlin, but once onboard for departure, I was assured by the flight crew that all connections would be made.

Feeling better, I got a little rest before we landed around 5 a.m. Reykjavik time. As we pulled up to the gate, all passengers scheduled for early morning connections were told to disembark first. We dashed out of the plane, only to find no airline staff were on hand to direct us to our departure gates. WOW!

We quickly found one of the digital flight monitors, and sprinted to our departure gate, only to discover the flight to Berlin was gone. WOW!

I told Ryan we should be able to catch the next flight to Berlin, but unfortunately, it wasn't until the next day—Monday morning. Ryan and I had a brief planning session that went something like this:

"Ryan, I don't have to be at the Conference until Tuesday. Let's stay in Reykjavik, it might be fun."

"But Dad, I was looking forward to our plans for Sunday and Monday. We have a walking tour, river cruise and plans to visit the Pergamon Museum. Besides Sunday and Monday are our only two days together before you have to work."

Our only two days together before you have to work. Okay. What parent would argue with that logic? Ryan was *looking forward* to our time together in Berlin and not just the few days he would be touring on his own.

Minds made up, we ran to the airport information desk to find out what the airline could do for us that day. The plan was already in place, apparently. Passengers traveling to Berlin were being routed to Paris. "But, what then?" I asked. "WOW doesn't fly from Paris to Berlin."

The attendant gave a vague remark about catching a 3 p.m. Delta flight to Berlin. I wanted to get more details, but we were running out of time to catch the flight. Under duress, we sprinted to the gate. About three hours later, we disembarked

Departing Charles De Gaulle airport in the "as-is" Skoda

A windfarm along the A1 Autoroute in northern France

Autobahn 1 tunnel, Cologne

in Paris only to learn that the Delta flight to Berlin was booked. WOW!

I went to the WOW desk in the baggage claim area, only to find them completely unhelpful. They had no idea how to help us get to Berlin and why we were sent to Paris in the first place. &#%@ WOW!

I found Ryan at the baggage carousel, and wasn't surprised that our suitcase failed to arrive. I was surprised, however, to find Ryan talking to James Madison University student **Sam,** who was also on this ill-fated flight to Berlin. About 21 years old, Sam seemed a bit scared. My fatherly instinct immediately kicked in: What if Ryan is stuck like this in the future, wouldn't I want a friendly stranger to help him? So, I told Sam to come with us and we'd figure something out together. His spirits rose immediately.

The three of us made our way through Charles De Gaulle airport—a labyrinthine structure that utilizes multiple buses and trains to move people between terminals. The fact all of us had been awake for over 24 hours (with only a little rest on the flight from D.C. to Iceland) did not help. After nearly an hour of getting on the wrong trains and buses, found the booking offices for the airlines that could get us to Berlin, only to learn all remaining flights that day were full. Giving up on air, I checked the train schedules on my smartphone. None could get us to Berlin in under 11 hours. By now, it was nearly 4 p.m. and not one member of our weary trio was interested in that.

Then it struck me. Three dudes, open roads, and beautiful countryside—rent a car! According to Google Maps, it would take nine hours to get to Berlin. With stops, I figured it would take 10 to 11 hours, but unlike the train, we could stop wherever and whenever we wanted.

Ryan and Sam were game, and Sam said he could even help drive. We made our way Budget Rental Car. The only affordable option was a just-returned Skoda, which we could take to Berlin for $600.00 "as is." In other words, they weren't going to clean the interior or inspect the exterior for damage. I took it. Fortunately, the car was clean, and I didn't notice any obvious scratches. Besides, in the United States rental companies no longer check returns with a fine tooth comb.

We hit the road for what turned out to be pure unscheduled joy with Ryan and our new friend, Sam. The drive from Charles de Gaulle through northern France to Belgium offered fantastic vistas as we drove through Forêt Domaniale d'Ermenonville, past countryside dotted with carefully manicured farms, and near cities and towns like Cambrai and Valenciennes. Along the way, we observed several wind farms, industrial areas, and power plants. An unexpected treat was the roadside service areas that offered selections of fresh food and delicious ham, turkey and cheese baguettes—served fresh and presented in ways unseen in U.S. highway rest stops.

The countryside was equally interesting in Belgium as we journeyed northeast to Liege. Soon after that, we crossed into Germany where, for the first time, I drove on a road with no speed limit. Heaven! We zoomed by more eye-catching country as well as the German cities of Cologne (driving through the autobahn 1 tunnel was amazing), Dortmund, and Hanover. It occurred to me that I'd have to fly back to Paris one day and retrace this trip, only taking time to explore many of the interesting cities we were zooming by.

Somewhere after Dortmund, Sam took over the driving and I was able to sleep for an hour. Around Hanover, I took back the wheel and pushed the car to its limit, making it to Berlin around 1 am. We took Sam to his student housing, which, as it turned out, was not far from the Hotel Estrel—home to the PDA Europe *Annual Meeting*. Ryan and I arrived at the Estrel around 2 a.m., and after a quick bite to eat, fell into some much needed slumber.

[Editor's Note: If you're following along our planes, trains and automobile theme, the drive to Berlin was the part of the movie when Steve Martin and John Candy are having fun and bonding in the motel, but more headaches were soon to follow. Read the full account in the online version of this "Tales from the Trail" at www.pda.org/pdaletter.**]**

TOOLS FOR SUCCESS

Brought to you by the PDA Career Center.
Go to www.pda.org/careers for the latest opportunities.

5 Ways to Make the Most of Your LinkedIn Group

Joshua Waldman, Career Enlightenment

IN 2006, when I still worked at Cisco, I started a little LinkedIn Group called "Cisco." Okay, not a very creative or original name, I'll admit. But I thought it was a good idea at the time to help Cisco folks leverage our mutual LinkedIn networks for career opportunities. HR didn't like the idea though—which naturally made me want to do it more!

Today, this group has over 17,000 people, grows by 100 people every week, and houses discussions about job postings, business strategy, and even sales on Cisco gear.

Recently, however, requests to join became overwhelming, and I "hired" a co-manager to facilitate the group.

What is a LinkedIn Group?

Simply put, groups allow people within the vast network of separated professionals on LinkedIn to connect on a single theme. Groups are a great way to network with new people minus the introductions or cold calling. Why? Because you have something in common.

Groups can be anything from alumni associations, professional associations, common interests, companies, and even subsets within companies. Hell, you can even create your own group in about two minutes.

Why Groups are a Great Job Search Tool

By joining and participating in a group, you (the jobseeker) have a powerful way of adding value to, and grow, your online reputation. As a group facilitator, I can tell you who are the leaders of the discussion, and who are the valued contributors to the group. When you participate, people notice.

Furthermore, by being members of the same group as your target company, your odds of getting a favorable response to your job inquiry are much higher.

5 Guidelines for LinkedIn Group Success

1. Join a group that takes you where you want to go, not one that keeps you where you are.

2. Join a group that you *will actually* participate in. Don't be a fly on the wall.

3. Participation in a group means posting and responding to discussion. Make sure you are putting your best foot forward, are positive, and show your motivation.

4. Tell your truth but don't shout! If you are unemployed, don't be ashamed and try to keep it a secret, but don't flaunt it either. Just be cool and make sure that you are always honest about where you are and what you are looking for.

5. Identify other leaders in the group and determine whether they could be valuable connections or information sources; if so, then by all means reach out to them.

[Editor's Note: Interested in joining a LinkedIn group? Look for the "PDA - Parenteral Drug Association" group on LinkedIn.**]**

About the Author

Joshua Waldman, author of *Job Searching with Social Media for Dummies*, is the founder of Career Enlightenment (careerenlightenment.com) which offers professional LinkedIn profile writing services and career advice for the modern jobseeker.

www.linkedin.com/company/pda

Aseptic Processing

2017 SCHEDULE

OPTION 1
Week 1: January 23-27
Week 2: February 20-24

OPTION 2
Week 1: March 27-31
Week 2: April 24-28

OPTION 3
Week 1: May 15-19
Week 2: June 12-16

OPTION 4
Week 1: July 24-28
Week 2: August 21-25

OPTION 5
Week 1: October 9-13
Week 2: November 6-10

FOR MORE INFORMATION CONTACT:
Kim McIntire
Assistant Manager
Laboratory Operations
Tel: +1 (301) 656-5900 ext. 103
E-mail: mcintire@pda.org

LOCATION:
PDA Training and Research Institute
4350 East West Highway, Suite 150
Bethesda, MD 20814
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-1093

The most comprehensive course in the preparation of sterile parenteral products

This two-week comprehensive course, taught by numerous industry leading experts in their fields, with more than 300 years of combined experience, will give you the training and information needed to properly evaluate and improve your aseptic processes to ensure sterile products. This course provides the perfect balance of hands-on laboratory and lecture training, equipping you with tools and practical experience you can apply immediately on the job.

YOU'LL LEARN HOW TO:

- Evaluate and improve current aseptic processing procedures at your facility
- Correlate basic microbiology concepts and techniques to multiple aspects of aseptic processing
- Evaluate your environmental monitoring program to collect appropriate data, identify and interpret trends
- Develop robust media fill protocols including appropriate interventions, observations and documentation procedures
- And much more!

SPACE IS LIMITED
Register Today
pda.org/2017Aseptic

*PDA **Education** – Where Excellence Begins*

PDA is accredited by ACPE and offers continuing education for professional engineers.

snapshot

PDA BioAB Members Keep Busy in First Half of 2016

John Geigert, BioPharmaceutical Quality Solutions

PDA's Biotechnology Advisory Board (BioAB) hit the ground running in the first half of 2016 and its activities continue to gain momentum. BioAB members help PDA establish its strategic direction and provide oversight for the Association's biopharmaceutical scientific and technical activities. The following are a few highlights of BioAB members' activities from the first part of the year.

In June, **Vince Anicetti,** Senior Vice President, Quality and Compliance, Coherus Bioscience, and **Stephan Krause,** PhD, Director, QA Technology, AstraZeneca Biologics, co-chaired the *2016 PDA Biosimilars Conference* in Baltimore. **Michael VanDerWerf,** Director, Regulatory Affairs, Teva, and **Laurie Graham**, PhD, Acting Director, Division of Internal Policies and Programs, OPQ, U.S. FDA, helped moderate the sessions. Over 120 attended the conference, representing a number of international companies actively pursuing manufacturing of biosimilars, leaving with a better appreciation of FDA's analytical comparability approach and its similarities and differences with EMA's approach. Following the conference, Stephan Krause and **John Geigert,** PhD, President, BioPharmaceutical Quality Solutions, taught two new biosimilar courses they had developed for the PDA Education program.

Also in June, **Karen Walker**, Global Head, Quality, Cell and Gene Therapies Unit, Novartis, covered how to manage raw material risks for cell and gene therapies at the *Advanced Therapy Medicinal Products* conference in Berlin. Here, attendees expressed the need for further PDA guidance to help better understand the challenges of taking one's product from development to the clinical stage. John Geigert also taught another PDA Education course in conjunction with this meeting. This was a new course on practical GMPs for ATMPs, adapted from GMP principles on proteins described in *PDA Technical Report No. 56: Application of Phase-Appropriate Quality Systems and CGMP to the Development of Therapeutic Protein Drug Substance.*

On the regulatory side, **Vijay Chiruvolu,** Senior Director, Kite Pharma, is now serving as team lead for PDA's review of the FDA draft guidance on Comparability Protocols. **Nadine Ritter,** President, Global Biotech Experts, is also serving as team lead of the PDA commenting team for the FDA draft guidance on analytical methods validation for immunological methods.

BioAB members reviewed and recommended for publication *Technical Report No. 74: Reprocessing of Biopharmaceuticals* and *Technical Report No. 75: Consensus Method for Rating 0.1µm Mycoplasma Reduction Filters.* Both were published this summer.

BioAB members continue to work hard for PDA. Please give them a round of thanks for their continuing service to you.

Journal *Preview*

September–October Issue of PDA Journal Covers 2015 Viral Clearance Symposium

In October 2015, industry and regulatory experts gathered to discuss critical viral clearance concerns in Cambridge, Mass. at the 4th *Viral Clearance Symposium*. The latest issue of the Journal features proceedings from this important meeting. Go to http://journal.pda.org

Conference Proceeding

Glen Bolton, Rich Levy, "Introduction: Proceedings of the 2015 Viral Clearance Symposium"

Junfen Ma, David Roush, "Session 1.1: Viral clearance using traditional, well-understood unit operations: Low pH and Detergent"

David Roush, Junfen Ma, "Viral clearance using traditional, well-understood unit operations", "Session 1.2: Virus Retentive Filtration"

Johannes Blümel, Kurt Brorson, "Session 2: Company specific data on cycled resin testing"

Chris Gallo, Dayue Chen, "Session 3.1: Protein A, Hydroxyapatite, and Mixed Mode Chromatography"

Dayue Chen, Chris Gallo, "Session 3.2: Viral Clearance of Emerging Unit Operations:"

Rachel Specht, Meisam Bakhshayeshi, "Rachel Specht, Meisam Bakhshayeshi"

Meisam Bakhshayeshi, Rachel Specht, "Session 4.2: Viral Spiking, Viral Preparation, and Upstream Risk Mitigation Strategies"

Glen Bolton, Johannes Blümel, "Session 5: Conference Summary: Key Discussion and Outcomes, Pending"

PDA Paper

Bob Buhlmann, Madlene Dole, Zena Kaufmann, "PDA Points to Consider: Fundamental Concepts in Data Integrity"

Which Test is Appropriate for Container Closure Integrity?

Paul Larocque, Acerna

Container closure integrity (CCI) testing is receiving more attention these days. In fact, the recently revised USP <1> *Injections and Implanted Drug Products (Parenterals)-Product Quality Tests,* specifies that "the packaging system should be closed or sealed in such a manner as to prevent contamination or loss of contents. Validation of container integrity must demonstrate no penetration of microbial contamination or gain or loss of any chemical or physical parameter deemed necessary to protect the product." This revision offers new insight into CCI testing ***(1),*** in spite of well established methods available, such as U.S. FDA guidance and PDA technical reports ***(2–6).***

These existing methods show CCI tests are used to measure moisture ingress into lyophilized products, moisture egress out of ophthalmic or blow fill seal products, oxygen ingress into products packaged under vacuum or nitrogen, and microbial ingress into sterile product.

Measuring Leak Rate is Critical

Gaseous leakage is a measure of the rate of gas flow through a leak path under specific conditions of temperature and the concentration or pressure differential across the barrier as measured in pascal cubic meters per second (Pa • m^3/s); the pressure differential (ΔP) is typically one atmosphere during the test ***(1).*** Here are three typical examples:

- When the shelf package has no headspace pressure differential (e.g., dry nitrogen atmosphere; ΔP = 0), diffusion of oxygen or H_2O gas into the package is typically the failure mode.
- When the shelf package has a headspace vacuum (i.e., total or partial vacuum; ΔP < 0), then measuring the increase in headspace pressure is typically done .
- When liquid leakage is studied, either as liquid escaping or microbial ingress, the absence of leakage is the critical quality attribute ***(1).***

Essentially, all pharmaceutical packages leak to some extent, thus a zero leak rate is not feasible or needed ***(1).*** For example, one drug product may be extremely sensitive to oxygen or moisture such that a leak rate close to zero is needed to maintain quality over the shelf life. Conversely, another product may also be sensitive, but to a lesser extent such that *some* leakage can be tolerated over the shelf life. Thus, a near-zero leak ➤

rate would be an unnecessary burden on the second drug product and would be neither science- nor risk-based. So, the *maximum allowable leak limit* becomes the critical quality attribute. When maintaining sterility and the integrity of the formulation (but not headspace) are requirements for rigid packaging, a leak rate of $<6 \times 10^{-6}$ mbar·L/s (He test) is typical. Keep in mind, failure modes may be exaggerated due to temperature changes, e.g., a room-temperature product subject to cooling or freezing during winter shipping.

When maintaining sterility, integrity of the formulation, and headspace necessary for rigid packaging, a lower leak rate may be needed. This would be product-specific, i.e., how much oxygen (and for how long) can the formulation tolerate? ***(1).***

For multiple-dose packages, both the shelf life and the in-use maximum allowable leakage limit need to be established since multiple-dose packages must meet their shelf-life specifications after years of storage and then must continue to do so for the last dose after being breached multiple times. For example, a ten-dose, multidose package with a 24-month expiration date must meet its shelf-life specifications in the 23rd month after nine doses have already been extracted; a proper CCI study would address this worst case scenario. In-use dye tests for resealability are typically conducted in this instance ***(7).*** For all packages, inherent package integrity must conform to the required product–package maximum allowable leakage limit.

There are various types of container-closure integrity tests. *Deterministic* tests give a definitive result and are typically physicochemical methods. *Probabilistic* tests carry an element of uncertainty; microbial methods are probabilistic as are some physicochemical methods. Either type can be quantitative or qualitative, destructive or nondestructive, and/or online or offline. Whatever type of test it is, as always, test method validation is needed.

Examples of each type ***(1)*** include:

- Deterministic Leak Tests
  - Electrical conductivity and capacitance (high-voltage leak detection)
  - Laser-based gas headspace analysis
  - Mass extraction
  - Pressure decay
  - Tracer gas detection, vacuum mode
  - Vacuum decay

- Probabilistic Leak Tests
  - Bubble emission
  - Microbial challenge, immersion exposure
  - Tracer gas detection, sniffer mode
  - Tracer liquid

There are also various package seal tests. These include closure application and removal torque, package burst, package seal strength, residual seal force, and airborne ultrasound ***(1).***

The preceding tests are selected based on the likely failure mode of the package. The typical failure modes for the major primary packages are:

- Ampoules are typically 100% leak tested on line for mechanical or thermal cracks and poor initial heat sealing

- Glass vials may suffer from nonround necks and/or nonround stoppers

- Flexible containers (e.g., large-volume parenteral bags) may have poor welding, thin spots in the sheet, and/or mechanical damage during handling or autoclaving

- Blow fill seal containers may have poor heat seals or physical damage during handling

- Prefilled syringes have various failure modes but the suppliers will have qualified them under various stresses; pharmaceutical companies must ensure such a package will withstand any product-specific stresses during transportation, such as pressure changes, vibration, and temperature changes (e.g., freeze-thaw, summer heat, etc.) ***(4)***

Container Closure Integrity over Shelf Life

The sterility test has been used as a CCI test for many years but suffers from severe flaws. For example, the test is prone to false positives and is essentially incapable of detecting anything but gross leakage (as the numbers in the next paragraph explain). The test is still with us because it remains the primary tool for testing sterility even though a passing result adds almost no assurance the lot is sterile. Conversely, a failing result must be taken as definitive—short of obvious contamination during the test. The probability of detecting a contaminated batch using the sterility test is expressed by the equation $p = n(1 - (1 - c))$, where p = probability of detection, c = true fraction contaminated, and n = number of units tested ***(8,9).***

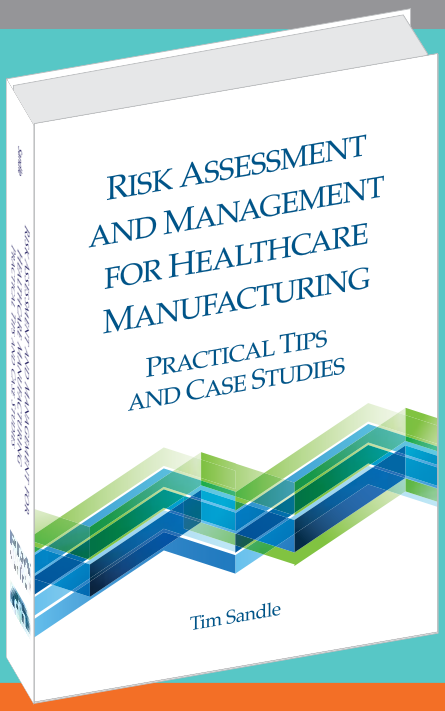
In a typical lot, it is apparent from media fills that the true fraction contaminated is less than one in 10,000 ($c < 0.0001$) and the number of units tested is typically 20. Thus, via the sterility test, the probability of detection of a contaminated unit in a typical lot is less than 0.002 (0.2%). Whenever a batch-release decision hangs on whether the lot is deemed sterile, the result of the sterility test is barely helpful, unless it fails.

Since the sterility test is so inadequate, using it as a CCI test during stability studies is unwise and raises a number of challenges. For instance, what does a failure at 24 months mean? Is your product's package unsound? Must a company recall every lot of every product in that container-closure system and develop new primary packaging? Is it wise to base such important considerations on a test that is outmoded, laborious, time consuming, prone to false positives, and expensive? Clearly, a proper CCI test should be used ***(5).***

The choice of a suitable CCI test is product and package-specific. Typically one or more of the deterministic or proba-

Continued at bottom of page 20

PDA Bookstore New Release



RISK ASSESSMENT AND MANAGEMENT FOR HEALTHCARE MANUFACTURING: PRACTICAL TIPS AND CASE STUDIES

BY: TIM SANDLE

PDA MEMBER PRICE: $240
PDA NON-MEMBER PRICE: $299
HARDCOVER: ITEM NO. 17337
DIGITAL: ITEM NO. 18018

Avoidance of hazards and assessment of risk have long been part of the manufacture of pharmaceuticals and healthcare products. Tim Sandle's newest book, *Risk Assessment and Management for Healthcare Manufacturers*, incorporates regulatory perspectives, scientific methods and practical examples to describe approaches to problem solving when assessing, managing and reviewing risks.

The book is divided into four sections that present a formal approach to risk. Sections focus on risk assessment and hazards; common risk assessment tools and problem-solving approaches; 'soft skills' that help in conducting risk assessments; and case studies exploring the problems and events that occur with pharmaceuticals and healthcare, against which the reader can consider real-life problems. The wide range of topics covered includes risk considerations for aging pharmaceutical facilities, application of quality risk management to cleanroom design and process incident investigation.

go.pda.org/RAMHM

www.pda.org/bookstore | Tel: +1 (301) 656-5900 | Fax: +1 (301) 986-1361

Manual (Sink) Materials Cleaning Process

The following blinded, unedited remarks are taken from PDA Connect℠, an online forum that allows PDA members to share some of the most challenging issues confronting the pharmaceutical industry. The discussions on PDA Connect℠ do not represent the official views of PDA, PDA's Board of Directors, or PDA members. The following is taken from the Process Validation Interest Group.

Questioner

Dear all,

In our facility, our WFI point of use has ambient temperature (+22°C).

Is it acceptable to perform hot tap water with cleaning agents and after that to use WFI for final rising?

Our proposal is to use WFI only for final rising to clean materials; afterwards these materials will be sterilized (autoclave).

Thanks in advance.

Respondent 1

If your procedure (SOP) is use in production is how your mentions, is acceptable, always that your validation area, validate it.

Respondent 2

Your proposal is possible but must be validated.

Respondent 3

From my experience, the procedure is acceptable when residue is acceptable.

Respondent 4

Per PDA *Technical Report 29: Points to Consider in Cleaning Validation,* the final rinse needs to be of the same quality as the water that will be used in the process. I've applied this in two ways. I've used a lower grade of water (e.g., USP Purified Water or RODI) with a final rinse of WFI on process equipment, and I've recirculated WFI to the first 10 stations of a vial washer and used virgin WFI on the final rinse stations. So long as your 55°C water meets the specifications of the water that wll be used on the parts, you are coverd in that regard.

I have far greater concerns on the "manual" part of your process. People are sufficiently variable that it is hard to declare any manual process to be qualified- people can be distracted, negligent, or just inattentive sometimes, and you'll get different results. Qualifying personnel variations is a high hurdle. I'd suggest an operation qualification process, in which operators need to pass a hands-on test based on the procedure and a high level of process monitoring- rinsate testing for conductivity if you're using detergents, or something appropriate to your cleaning process- to add detectability to failure modes.

Good luck!

Which Test is Appropriate for Container Closure Integrity? continued from page 18

bilistic tests discussed above are chosen as candidates and validated for use for the packaging configuration. The CCI test for an ambient-headspace, aqueous, 5 mL fill in a 5 mL glass vial with rubber stopper and aluminum seal drug product might be quite different from that for a dual-chamber, prefilled syringe with a lyophilized cake in one chamber and an aqueous solution in the other. Similarly ampoules and blow fill seal packages will require significantly different CCI tests.

In short, for parenteral products in particular, and liquid products in general (but also any other dosage form prone to container-closure failure modes during the shelf life), a proper CCI test provides assurance about the drug product post-launch, thereby reducing corporate risk of compliance events. Since USP has recently boosted its CCI content, it can be assumed that regulators will soon begin giving the matter even more attention than it is already receiving during application reviews in Washington, D.C., and by investigators while doing onsite inspections ***(5,6).*** Companies are wise to anticipate this and begin addressing it internally.

References

1. USP <1207> *Sterile Product Packaging—Integrity Evaluation*
2. Forster, R., *et al. PDA Technical Report No. 27: Pharmaceutical Package Integrity,* 1998
3. PDA, *Aspects of Container-Closure Integrity*, Technical Information Bulletin No. 4
4. Forster, R., et al. *PDA Technical Report No. 73: Prefilled Syringe User Requirements for Biotechnology Applications.* Bethesda, PDA, 2015.
5. Guidance for Industry – Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products, U.S. FDA, February 2008
6. Inspector's Technical Guide, Leak-Testing Sealed Ampoules of Parenteral Solutions, U.S. FDA, April 28, 1972
7. USP <381> Elastomeric Closures for Injections (Functionality Tests, Self-Sealing Capacity)
8. Sadowski, M., et al. *PDA Technical Report No. 30: Parametric Release of Pharmaceuticals and Medical Devices Terminally Sterilized by Moist Heat.* Bethesda, PDA, 2012.
9. Larocque, P., "Inconsistent Expectations Clash with Industry Best Practices for Sterile Products," *PDA Letter* 51 (June 2015): 20–24, 41.

About the Author

Paul Larocque is the President of Acerna Inc., a biological, pharmaceutical, and medical device consultancy specializing in aseptic processing and GMP services.

Annual Meeting to Highlight Next Gen Manufacturing

Madlene Dole, Novartis

Bill Gates famously said, "Never before in history has innovation offered promise of so much to so many in so short a time." This is considerably true for the pharmaceutical industry today. After all, it is in this sector where innovation can have a significant impact on the health and wellness of millions of people.

2017 PDA Annual Meeting and PDA Education courses

Anaheim, Calif.
April 3–7
www.pdaannualmeeting.org

Breakthrough advances in science and technology have led to the development of innovative therapies that require unique development, processing, and logistics. Automation, Big Data, the Internet of Things, robotics, continuous manufacturing, and more, all have a role to play in ushering in these new therapies, as well as significantly transforming the traditional pharmaceutical industry.

PDA remains committed to developing scientifically sound, practical technical information and resources to advance science and regulation worldwide. The *2017 PDA Annual Meeting* is no exception. With its theme of "Manufacturing Innovation: The Next Wave of Sterile & Biopharmaceutical Science, Technologies and Processing," innovation is at the heart of the conference.

Many of the sessions in this year's program will focus on Next Generation manufacturing technologies. Future facility design will drive both plenary and concurrent sessions. Technical emphasis will be on flexible manufacturing strategies, continuous manufacturing, and personalized medicine. Advancements in scientific discovery will also be discussed, including such recent advancements as gene editing tools, immunotherapies, and new technologies for delivery systems.

The *2017 PDA Annual Meeting* is taking shape as an outstanding program offering learning and networking opportunities spanning a wide array of critical and informative topics, all of which are linked to offering novel drug products to patients worldwide. Don't miss this outstanding event!

The Role of a Person in Plant for Early Development Projects

One Company's Experience

Xiaona Jing, Jesper Valbjørn, Pernille Hemmingsen, Christian Cimander, Genmab A/S

Trust is important in any relationship, particulary the relationship between a sponsor company and a contract manufacturing organization (CMO). As outsourcing becomes ever more important in the biopharmaceutical industry today, the effective management of CMOs is a topic of high interest. Many of the pioneers from both the customer and CMO sides gathered at the 2014 PDA *Outsourcing/Contract Manufacturing* conference in Berlin to answer the question, "Is outsourcing your weakest link?"

The concept of the "Person in Plant" emerged as a strongly debated topic at this conference. As an international biotechnology company with 15 years of outsourcing management experience, Genmab presented its own CMC collaboration philosophy, especially the experience of designating a Person in Plant for early development projects. By assigning a Person in Plant, Genmab has been able to develop a more trusting relationship with their CMO partners.

Article at a Glance

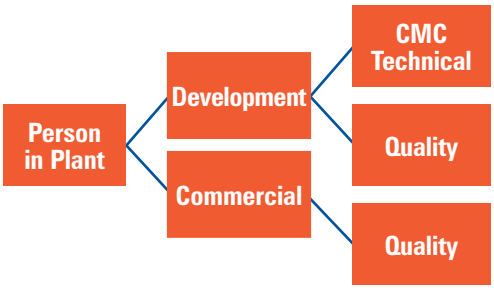
- Person in Plant encourages knowledge sharing and collaboration, but is not well understood
- Genmab shares its successful approach
- Selected individuals must avoid impacting the CMO's processes

The Dilemmas Around Person in Plant

There is no widely agreed definition for Person in Plant, which is partly the reason for the confusion around the term. From the wording, the term refers to having a project sponsor's employee or designee present at a contract manufacturing site in order to observe operations. Preferably, this is one person or just a few people, as a big group is difficult to manage in a production environment.

The actual scope of the Person in Plant depends on the stage of the project/product, as outlined in **Figure 1.**

Figure 1 Role of the Person in Plant in the Product Lifecycle



Sponsor companies have to make several risk-based decisions when considering whether to assign an employee to observe the CMO's operations. This is most challenging for small, virtual companies that must decide on the efficient use of limited in-house resources versus the need for control.

ICH Q10, EU GMP Chapter 7 and *Eudralex* Volume 4 Chapter 7 all state that the pharmaceutical company/sponsor is ultimately responsible for ensuring control of production and product quality in outsourced operations. The U.S. FDA regards independent contract facilities "as an extension of the manufacturer's own facility." This is in line with the general expectation that accountability for product quality and patient safety lies with the sponsor company.

Though the sponsor has regulatory accountability, the question for small companies is how to stay in control with available resources? EU GMP Chapter 7 says

The purpose of a Person in Plant is to improve mutual understanding of the product and processes

that these processes "should incorporate *risk management principles*" (italics added for emphasis). Supplier controls must be based upon an evaluation of the risk of the supplier and its impact to product quality, safety and efficacy.

Mixed expectations between the two contractual parties present another issue for the Person in Plant. This individual has to meet the needs and expectations of both the customer and the CMO **(Figure 2).** Expectations may differ, even from the stakeholders within one party; nonetheless, it is important to find common ground to satisfy all parties.

The Value of a Person in Plant

The potential benefits of a Person in Plant, if managed properly, include knowledge sharing and collaborative troubleshooting—valuable for both sides. While the sponsor has extensive product knowledge from the product development experience, the CMO knows the ins and outs of their own facility, equipment, and processes.

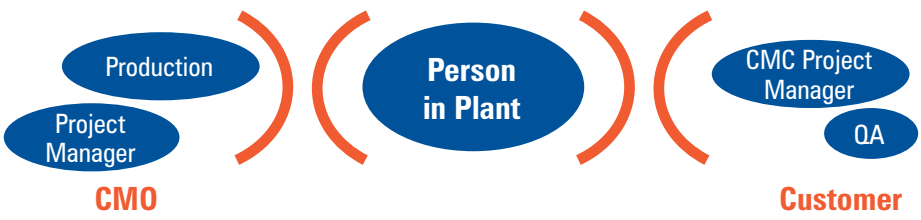
When sudden changes or unusual observations happen in production, the right representative from a sponsor could support troubleshooting due to their knowledge of the specific product, such as the molecular structure and properties, the formulation and process, etc. For example, forced degradation study data could indicate the sensitivity of the molecule to different stress factors such as pH, agitation, freeze thaw, light, oxygen, shear stress, etc. Likewise stability data, including real temperature and accelerated conditions, could support reevaluating the manufacturing holding time and shipping temperature in light of deviations and excursions.

Furthermore, regulators expect companies to regularly work toward continuous learning and improvement of the manufacturing process. FDA guidance on the lifecycle approach for process validation details a three-stage collaborative/continuous learning and improvement process comprised of Design (Stage 1), Process Qualification (Stage 2), and Continued Process Verification (Stage 3). While admitting the value of this approach, the biopharmaceutical industry—especially small, virtual companies—is trying to determine how to best implement this approach, given the resource restrictions. Regarding this quandary, **Jeffrey Baker,** Director of Office of Biotechnology Products (OBP) in FDA, once stated that it is "all about understanding your process." A Person in Plant could be beneficial for a sponsor to better understand the actual manufacturing process at the CMO, e.g., facility design, workflow, etc. This process understanding not only makes it much easier to review/approve the process descriptions/batch records, but also clarifies what in-process controls are available, if "blind spots" exist, where the risks are higher and how the CMO controls these risks, etc.

Only One Tool in the CMO Toolbox

For Genmab, a Danish biotech company specializing in antibody therapies, Person

Figure 2 Mixed Expectations for Person in Plant from Internal and External Stakeholders



2016 PDA Upcoming Events

SAVE THE DATE for PDA's 2016 Events

OCTOBER

17-18
2016 PDA Universe of Pre-filled Syringes & Injection Devices
Huntington Beach, CA
pda.org/2016Prefilled

17-19
DSP – Purification of Biomolecules
In Cooperation with DECHEMA
Clausthal-Zellerfeld, Germany
pda.org/EU/DSPBio

17-21
SOLD OUT
2016 Aseptic Processing Training Program – Session 5 Week 2: November 7-11
Bethesda, MD

19
2016 PDA Drug Delivery Combination Products Workshop
Huntington Beach, CA
pda.org/2016Combo

19-20
CBP – Continuous Bioprocessing of Biomolecules
In Cooperation with DECHEMA
Clausthal-Zellerfeld, Germany
pda.org/EU/CBPBio

20-21
2016 PDA Universe of Pre-filled Syringes and Injection Devices Course Series
Huntington Beach, CA
pda.org/2016PFSCourses

24
Particle Identification in Parenterals
Berlin, Germany
pda.org/EU/TCParticleIdentification2016

24-26
11th Annual PDA Global Conference on Pharmaceutical Microbiology
Arlington, VA
pda.org/2016Micro

25-26
Visual Inspection Forum
Berlin, Germany
pda.org/EU/VisualInspection2016

25-26
NEW COURSE
Isolator Technology
Bethesda, MD
pda.org/2016Isolator

26-27
ARLINGTON – 2016 PDA Workshop: Current Challenges in Aseptic Processing, Potential Changes in EMA/PIC/S Annex 1 Revision
Arlington, VA
pda.org/2016Annex1East

27
Testmethoden für vorbefüllte Spritzen (PFS)
Berlin, Germany
pda.org/EU/TestMethodenPFS

27-28
An Introduction to Visual Inspection: A hands-on course
Berlin, Germany
pda.org/EU/TCVisual2016

27-28
11th Annual PDA Global Conference on Pharmaceutical Microbiology Course Series
Arlington, VA
pda.org/2016MicroCourses

NOVEMBER

2
2016 PDA Outsourcing/CMO Course Series
Washington, DC
pda.org/2016CMOCourses

3-4
2016 PDA Outsourcing/CMO Conference
Washington, DC
pda.org/2016CMO

8-9
BERLIN – 2016 PDA Data Integrity Workshop
Berlin, Germany
pda.org/2016DataBerlin2

14
Managing Single- and Multi-Source Supply Chain Challenges
Barcelona, Spain
pda.org/EU/TCOutsourcing2016

14-16
Human Factors Week
Bethesda, MD
pda.org/2016HumanFactorsWeek

Denotes Laboratory Courses | Denotes Lecture Courses

1946
70TH ANNIVERSARY
2016

PDA®
Parenteral Drug Association

For an updated PDA calendar of events, please visit:

pda.org/calendar

15-16
PDA Europe Outsourcing & Contract Manufacturing
Barcelona, Spain
pda.org/EU/Outsourcing2016

17
Quality by Design for Biopharmaceuticals
Barcelona, Spain
pda.org/EU/QBD2016

17-18
Basics of Successful Auditing
Barcelona, Spain
pda.org/EU/Auditing2016

17-18
Outsourcing, Technology Transfer and CMO-Client Relationships
Barcelona, Spain
pda.org/EU/CMO2016

17-18
Practical Guide for Root Cause Investigations – Methodology & Tool Kit
Barcelona, Spain
pda.org/EU/RootCause2016

17-18
Risk Management in Technology Transfer
Barcelona, Spain
pda.org/EU/Risk2016

17-18
Single Use Systems for the Manufacturing of Parenteral Products
Bethesda, MD
pda.org/2016SUS

24-25
Track und Trace Implementierung von Serialisierung, Fälschungssicherheit und Verifizierung für pharmazeutische Produkte
Leipzig, Germany
pda.org/EU/Track-und-Trace2016

28 – Dec 1
Facilities and Engineering Week
Bethesda, MD
pda.org/2016FacilitiesWeek

DECEMBER

5-8
SOLD OUT
Fundamentals of Aseptic Processing
Bethesda, MD

5-8
Lyophilization Week
Bethesda, MD
pda.org/2016Lyo

7-8
SAN DIEGO – 2016 PDA Data Integrity Workshop
San Diego, CA
pda.org/2016DataWest

9
2016 Data Integrity Workshop Course Series
San Diego, CA
pda.org/2016DataCourses

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

Twitter at
@PDAOnline

LinkedIn at
LinkedIn.com/company/PDA

PDA Connect℠
@PDA Connect ℠
PDA's members-only online discussion forum

in Plant is just one part of their collaboration strategy with CMO partners. Based on 15 years of outsourcing management experience, Genmab has established its own CMC collaboration philosophy. In brief, this approach requires Genmab to:

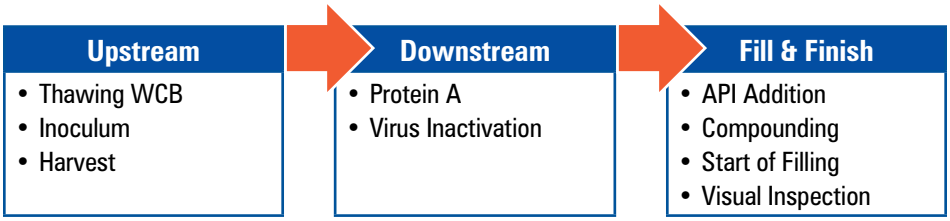
- Establish direct communication lines—no funnelling
- Leave disputes to the responsible contract manager to resolve contract issues —keep it out of the technical teams
- Evaluate performance (quality, timeliness, cost transparency, etc.) and re-align expectations every 6–12 months in steering committee meetings
- Arrange face-to-face meetings and build relationships

As for the Person in Plant, Genmab's internal guideline specifies that the CMO **can** be visited by the designated Person in Plant, "during production at **critical stages** of the manufacturing process or for evaluation of data. A brief visit report is then created." The company believes that through personal interaction and communication in manufacturing plants, the manufacturing process for the specific product can be optimized for the best possible outcome and the CMO's understanding enhanced.

Yet the individual designated as the Person in Plant must be careful to avoid actions, even inadvertent ones, that could shift liability from the CMO to Genmab, e.g., if they give instruction or participate in processing the product, they could unintentionally provide guidance conflicting with the CMO's practices, possibly leading to in-process deviations of a product. The GMP responsibility of ongoing production always remains with the CMO.

When is a Person in Plant needed? For Genmab, this depends upon the specific project's risk assessment, CMO and process. Very often a Person in Plant will be required for initial batches (first 1–3 batches), especially when critical steps or safety-related stages are involved during upstream, downstream, or fill/finish unit operations **(Figure 3).** Afterward, the Person in Plant approach might be used if the process changes, during technology transfer or unexpected issues arise.

Figure 3 The Common Examples of Important Manufacturing Steps to Consider Person in Plant for a mAb Product



Who can be designated as a Person in Plant? For the development project, this individual should preferably be selected from those actually involved in the specific product development from the CMC technical team. Occasionally, the responsible QA could also join to observe the operations at the CMO, depending on the stage of the collaboration or project stage. Keep in mind, that the purpose of a Person in Plant is to improve mutual understanding of the product and processes, not to perform an audit during the visit. Ultimately, a sponsor company's Person in Plant should:

- Be part of risk-based supplier oversight, i.e., the right person in the right place at the right time
- Communicate in an appropriate manner, showing respect and trust.
- Choose the right communication channel, perhaps through the CMO project manager or supervisor, but avoid direct communication with CMO plant operators unless mutually agreed.
- Refrain from interfering with operations at the contractor site (this creates legal liability)

Conclusion

In short, the Person in Plant approach is part of joint product and process understanding. It is only one of the tools available to building effective partner relationships. Establishing and maintaining a long-lasting partnership relies on mutual understanding. And understanding is the first step to trust. There is an old Chinese proverb, *"Work with who you trust, and trust who you work with."* Designating a Person in Plant is one way to build that trust.

[Editor's Note: Learn more about Person in Plant and other strategies for working with your CMO in the PDA Education course "Establishing a Robust Relationship with Your Client/CMO" after the *2016 PDA Outsourcing/CMO Conference.***]**

About the Authors

Xiaona Jing was leading pharmaceutical development and drug product manufacturing through global management of contract organizations and outsourcing activities in Genmab. Currently she works at Roche.

Jesper Valbjørn has over 20 years of experience within CMC development in the biopharmaceutical industry holding extensive experience in outsourcing and collaboration with CMOs.

Pernille Hemmingsen holds broad pharmaceutical development experience within both oral solid dosage forms and injectables. Particularly driving innovative product ideas into clinical development has been her focus.

Christian Cimander has over 15 years of experience in the biopharmaceutical industry. Christian is currently Director of CMC at Genmab.

ELIMINATE PARTICULATES & FIBERS IN THE CORE.

SYNTHETIC WRITING SUBSTRATE

CleanPrint 10

- Low particulate and non-shedding
- Exceptionally durable
- Abrasion and chemical resistant
- Easy to write on
- Double bagged packaged sterile

CUSTOM DOCUMENTATION

Core 2 Write

- Logbooks, ID tags, Forms and Labels
- Constructed using CLEANPRINT 10
- Customized specifically per customer
- Individual unique numbering and integrity features
- RFID Technology available

HEPA FILTERED PRINTING SYSTEM

Core 2 Print

- Print wirelessly into cleanrooms
- Use with pre-sterilized CLEANPRINT 10
- 316L Stainless Steel Construction, can be completely disinfected
- HEPA Filter cabinet
- Sheet fed, high speed digital printer using chemical resistant ink

vai
VELTEK ASSOCIATES, INC.

15 Lee Boulevard
Malvern, PA 19355-1234 USA
(610) 644-8335

www.sterile.com

Microbiologists: Get to Know Manufacturing's Raw Material Suppliers

Christine Massaro, Johnson & Johnson

A raw material OOS result is a stressful undertaking for all involved

It seems that as a whole, the relationship between microbiologists and our suppliers is backward. Instead of developing a consistent relationship complete with constant communication, most of us microbiologists only contact our raw material suppliers when a catastrophic problem arises, such as an out-of-specification (OOS) result.

At any given product manufacturing plant or quality control testing lab, raw materials seem to routinely come and go. The materials get produced, delivered to your site, sampled, tested, and the results reported to Quality for release. This process repeats itself dozens, if not hundreds of times, until the "dreaded" OOS result occurs.

This scenario usually plays out like this:

A lab manager for a finished product manufacturing plant receives word of an initial raw material OOS from one of their staff. After a preliminary review, the results appear valid. A sense of doom rolls in as the manager knows what's coming next. An official notification is sent to Management and the sky begins to fall. The manager now fields questions from Quality, Planning, Supply Chain, Finance and other departments they did not even know existed. As luck would have it, the manager then finds out this particular raw material lot has been received and released a few times before at their site and used to manufacture other finished product lots already released to market.

At this point, the manager initiates a lengthy investigation involving the raw material vendor site and the microbiology lab and impact assessments.

If you've been through this scenario, you know that it often feels like you are on your own as you try to lead the investigations in the lab and the raw material manufacturing site and provide guidance to the supplier and your own management. You may even get close to a probable root cause of the excursion, then subsequently patch together a series of corrective and preventive actions (CAPAs) at the supplier's plant, throwing in some at your own site's lab for good measure since you can always find "opportunities for improvement."

You then hope that all these CAPAs work, since no one wants to repeat this process nor deem a CAPA "ineffective." In the wake of all this, there are potential product quality impact, manufacturing delays, financial loss, potential compliance issues, an audit trail for inspectors, and product supply chain shortages. If you do not come up with probable root cause, it goes into the abyss of unsolved cold case files of microbiology failures, and the inevitability of material destruction.

Microbiologists Need Macro Role

During the investigation process, it is not uncommon to find shortcomings in the existing Quality and Supply Agreements.

The way these agreements are produced is analogous to meeting a stranger, blindly signing a prenuptial agreement that someone else authored, immediately getting married, and hoping for the best. Then, when it becomes clear that the relationship isn't going as hoped, finding the prenuptial agreement locks both parties into the commitment, painfully waiting for the contract to expire.

Frequently, we take this exact approach with our raw material vendors: we sign up, order, receive, test, and hope. We only fully realize what we signed up for when we need to dig out the agreements and then find we have limited ability to intervene or refine processes and procedures afterward.

Failure to set vendor expectations, or a misalignment in specifications across testing sites among the vendor, their lab and a contract manufacturing organization (CMO) often cause discrepancies usually discovered for the first time during an investigation. Typically, the Certificate of Analysis (CoA) is sent along with the raw material from the vendor, received by the CMO's lab, then the raw material is tested again and results in recovery of an objectionable organism, setting off the OOS process as described earlier. This typically halts production and everything downstream.

As microbiologists, we are often left to figure out the broken pieces and put them back together after the storm.

If we have the expertise and the knowledge to put the pieces back after the fallout, one can only wonder why we are not involved in the quality/supplier agreement process in the first place. Microbiologists need to get out there on the plant floor at the supplier, learn the process, help define the process, and redefine as needed. The vendor vetting process and expectation setting needs to start way before signing those agreements on the dotted line.

Treat Your Suppliers Like CMOs

We often invest a substantial amount of time choosing finished product CMOs wisely. We audit, perform risk assessments, review cleaning and sanitization adequacy, and understand their regulatory history. We inspect their labs and go on plant tours. We perform due diligence visits before, during and after product launch. We may even have a Person in Plant.

We don't seem to do this at all, however, with our raw material suppliers. For many suppliers, a "desktop" audit is all that's performed with check box Q&A. This is all standard protocol, but what we really need to know is, can the vendor consistently provide quality raw materials that meet specified standards, and provide a solid commitment that they will cooperate when issues arise? Specifically, will they work in conjunction

with you on corrective actions resulting from investigations that may be warranted?

Much like any relationship, working with your vendor requires constant communication throughout the life of the relationship and clear expectations beforehand. Once you have identified prospective vendors, understand if contacts including Quality and Account Managers will be assigned. Provide input in setting up Service/Quality Agreements and include expected audit frequencies, for-cause audit clauses and risk assessments visits as needed.

Although an onsite risk assessment for each vendor may not be practical, identifying high-risk vendors may be prudent. An assessment can be performed based on material origins (plant, animal etc.), water activity, material bioburden requirements (needed for irradiation, filtration), material manufacturing process (steam treated, spray dry), finished product formulation, (infant, compromised patient), low level preservative product, etc.

If at all possible, go out and audit the plant. Ideally, a microbiological risk assessment should be performed as if it were a finished product CMO, including:

- Equipment train setup
- Cleaning and sanitization processes
- Water system walkthrough
- Quality Control testing
- Raw material receipt and handling
- Review of their internal and external audit practices
- Personnel training and education

The supplier relies on a CoA to release their product to you. The CoA is their objective evidence that the material meets specification. Does the supplier have someone on their staff who understands the microbiology results they receive and do they review the suitability reports to ensure that the studies are performed correctly? I often see vast differences when comparing the manufacturer's contract lab test methods to the receiving facilities' microbiology lab test methods. Although all may be performed using standard USP methods, there can be significant variability within the methods including the use of neutralizers, different dilution schemes, additional tests being performed if over and above the compendial recommended testing, and different approaches to the identification of organisms if recovered.

The way these agreements are produced is analogous to meeting a stranger, blindly signing a prenuptial agreement that someone else authored, immediately getting married, and hoping for the best

OOS results and subsequent investigations can lead to review of these test methods late in the game only to find out the testing is very different. While we know microbial contamination is often not uniform throughout a batch or given container, it doesn't help matters during an investigation when labs are testing vastly different methods and you are reviewing very different results. The result from the vendor's CoA should also be reviewed periodically. I often see companies whose quality units are unaware that there is consistent microbial recovery in their raw materials until there is an investigation and historical data needs to be reviewed. The trending program should include a review of the level and organism types. Theses reviews should occur quarterly with an eye toward potential adverse trends in the manufacturing process or microbial quality of the starting raw material. Often, the results stay at the level of the Quality inspector on incoming at the manufacturing plant. As long as the material meets the specification, it's released. Results then become buried in the batch record. Tracking the level of microorganisms and/or type of microorganisms recovered in your materials may provide some insight into the manufacturing process or controls and the supplier over time.

Conclusion

It is important perform detailed due diligence prior to choosing your suppliers. Perform risk assessments, be clear on your specification requirements with your supplier, request additional processing steps or changes if necessary, monitor the results from your vendor over time and communicate any potential issues or concerns early and often. Most importantly, carefully craft supplier agreements and get the microbiologists involved! It may seem like a great amount of work, but it can help prevent the "dreaded" OOS and ensure quality raw materials and uninterrupted supply chain in the years to come.

About the Author

Christine Massaro has 16 years of manufacturing and microbiology experience in the pharmaceutical/biotechnology industry with increasing levels of responsibility.

SAMSUNG

SAMSUNG BIOLOGICS

Aseptic Fill & Finish at SAMSUNG

Engineered for Quality

CMO LEADERSHIP AWARDS 2016

CATEGORIES
- QUALITY
- CAPABILITIES
- RELIABILITY
- COMPATIBILITY

Common CMO Audit Allergens

Audits of a contract manufacturing organization (CMO) are stressful for everyone. There are a number of common "allergens," impacting both the auditor and the host company. But there are some Rx available to prevent these allergens.

Are you a CMO or auditor with the following symptoms?

Lying

The quickest way to destroy a relationship

"Rocket" Tours

Abbreviated facility tours that skip parts of the operation

Confusing Observations

Often caused by incomplete auditor notes or miscommunication by the CMO

Ignoring Company Rules

Restrictions may include smoking, photography, cell phones, jewelry, cosmetics, clothing, and movement

Rx for these Common Audit Allergens

Good Relationships

Establishing a good working relationship between both parties that includes systematic communication

A Robust Quality Agreement

Outlines specific roles for the CMO and host company

Reference

1. Thorpe, T.L., and Walker, J. "Auditing the CMO." In *Pharmaceutical Outsourcing: Quality Management and Project Delivery,* eds. Trevor Deeks, Karen Ginsbury, and Susan Schniepp, 379–404. Bethesda: PDA/DHI, 2013.

PDA
Parenteral Drug Association

The Parenteral Drug Association presents:

2016 PDA Europe

Outsourcing & Contract Manufacturing

14 November
Risk-based Approach for Prevention and Management of Drug Shortages

17 November
Quality by Design for Biopharmaceuticals

17-18 November
Practical Guide for Root Cause Investigations – Methodology & Tool Kit

17-18 November
Outsourcing, Technology Transfer, and CMO-Client Relationships

17-18 November
Risk Management in Technology Transfer

17-18 November
Basics of Successful Auditing

Register by 15 Oct 2016 and SAVE!

15-16 November 2016

Olivia Balmes Hotel

Barcelona | Spain

pda.org/EU/Outsourcing2016

snapshot

PDA Program to Address Post-Approval Hurdles

A Call to Action

PDA Post Approval Change: Innovation for Availability of Medicines (PAC iAM℠) Task Force

The seamless delivery of high quality, effective and safe medicines to patients is the primary responsibility of every pharmaceutical company. Doing so, however, is by no means effortless. Just look at any of the lists of drug shortages on the websites of global regulators. The lists are too long and include too many critical therapies.

The availability of medicines is challenged by a variety of factors, one of which is global supply chain segmentation due to global regulatory hurdles imposed on product-related post-approval changes (PACs).

Across the globe, regulatory PAC processes can be characterized as complex and inconsistent

Manufacturing changes are performed for several reasons. New and updated regulatory requirements must be implemented in order for companies to remain compliant. During the commercial lifecycle of a product, companies naturally gain more knowledge which can be used to improve the manufacturing process and/or analytical methods. In addition, changes in suppliers, evolution of technologies, innovation, ongoing risk management, and continual improvement can also result in PACs.

Today, most companies operate globally; therefore, PACs are intended to apply globally. Many require approval, however, by the national regulatory authority of each country before the company can deliver a product manufactured using improved processes. In practice, this can result in submitting change filings for assessment to more than a hundred individual regulatory bodies. Across the globe, regulatory PAC processes can be characterized as complex and inconsistent due to varying classifications, different submission requirements, and lengthy implementation timelines (it is not uncommon for a simple change to take more than five years to receive approval). All of these complexities create a disincentive—albeit unintentional—for manufacturers to integrate growing product and process knowledge, continually improve, or innovate technologies. The current PAC environment also represents a challenge for standardizing the implementation of a regulatory change across multiple countries. This forces companies to segment their inventory for different markets, leading to increased costs for inventory, manufacturing, and testing, and reduces the company's ability to respond to sudden demand changes in a timely and predictable manner.

Companies actually want to innovate and improve on top of maintaining compliance with current regulations. But in order to avoid the burden of implementing changes in such a complex process, many find it easier to postpone improvements to facilities, processes, and analytics, or simply refrain from planning advancements at all.

Segmentation of inventory and disincentives for continual improvement results in the unintended consequence of drug shortages.

PDA Task Force Seeks Comprehensive PAC Reform

If the current state of country-specific requirements continues, innovation will stop, drug shortages will increase, and the patients who depend on these drugs will be the ones who lose. It is time for both industry and regulators to transform the current paradigm for PACs.

This is a call to action to:

- Accelerate awareness of the current challenges of PACs and activate a dialog at a broader industry and regulatory scale to drive significant change
- Apply science and risk-based approaches to change management in order to expedite PACs and reduce the global regulatory filing burden
- Demonstrate streamlined PAC processes to enable international regulatory convergence and mutual reliance for improved availability of medicines to patients

The industry must do its part to contribute to this broad and sweeping reform for PAC. PDA's Post Approval Change: Innovation for Availability of Medicines (PAC iAM℠) Program will identify, assess, and address current barriers to implementation of PACs. Specifically, PDA is working on the following deliverables:

- Publication of science- and risk-based approaches to lifecycle management
- Templates for standardized global post-approval change management protocols (PACMPs) for specific changes to manufacturing processes and analytical technologies
- A library of real world examples of best practices for PACs using a science- and risk-based approach
- Forums to encourage collaboration and open dialog among stakeholders in healthcare

PDA appreciates and supports ongoing activities that streamline PAC approval, including the efforts on ICH Q12: *Tech-*

nical and Regulatory Considerations for Pharmaceutical Lifecycle Management, and the World Health Assembly resolution on strengthening the regulatory system for medical products ***(1).***

PDA would like to see timelines for the implementation of global PACs reduced from years to months. This should incentivize innovation and continual improvement within the industry and enable uninterrupted supply of medicines to patients.

PDA is currently looking for volunteers to develop a PDA technical report on PACs and product lifecycle management (LCM), and to catalogue examples of practical application of global Post Approval Change Management Protocols (PACMPs).

Post Approval Change: Innovation for Availability of Medicines (PAC iAM) Task Force members

Anders Vinther, PhD, Sanofi-Pasteur (chair)
Emma Ramnarine, Genentech (co-chair)
Ursula Busse, PhD, Novartis
Franck Chassant, Sanofi-Pasteur
Marcello Colao, GSK Biologicals
Julia Edwards, Biogen
Maik Jornitz, G-Con LLC
Marina Kozak, Friends of Cancer Research
Morten Munk, NNE Pharmaplan
Melissa Seymour, Biogen
Mihaela Simianu, Consultant
Lisa Skeens, PhD, Hospira
Denyse Baker, PDA

PDA seeks individuals with experience in PAC from a development, manufacturing, analytical, change control, manufacturing science and technology, or regulatory CMC perspective in all aspects of manufacturing (small molecules, generics, biologics, etc.). If you are interested in participating on the team developing the technical report or want to help identify specific global PACMPs, please email PDA's Science and Regulatory Affairs department at sci_reg@pda.org.

Reference

1. WHA 67.20 – Regulatory System Strengthening for Medical Products. WHA Resolution; sixty seventh World Health Assembly, World Health Organization, May 24, 2014

Regulatory Briefs

Regulatory briefs are compiled by PDA member volunteers and staff directly from official government/compendial releases. Links to additional information and documentation are available at www.pda.org/regulatorynews.

North America

FDA Seeks to Change GLPs

In August, the U.S. FDA proposed amending its Good Laboratory Practice (GLP) regulations to require a complete quality system approach for nonclinical laboratory studies. This approach is called a GLP Quality System and features safety and toxicity studies used to support product submissions to FDA. The Agency also seeks to revise the definition of a "testing facility" in light of current practices, such as multisite studies. This proposed revision is intended to build quality into nonclinical laboratory studies and help ensure data integrity.

Comments are due Nov. 22

FDA/EMA Discussions Include MRI

Over the summer, members of the U.S. FDA met with several European Union regulatory counterparts and stakeholders in Brussels to discuss ways to strengthen their shared commitment to product safety and public health. Discussions covered global supply chain issues, globalization of drug development, and the Mutual Reliance Initiative (MRI). Toward the conclusion of the trip, FDA officials reviewed EMA's mutual reliance plans. Both agencies expressed hope to continue regulatory alignment.

FDA Opens New Oncology CoE

FDA Commissioner **Robert Califf,** MD, selected **Richard Pazdur,** MD, as acting director of the Agency's new Oncology Center of Excellence. This Center of Excellence will serve as a central locus where regulatory scientists and reviewers with oncology clinical expertise in drugs, biologics and devices will collaborate and support an integrated approach to the advancement of cancer treatment.

Key Regulatory Dates

Comments Due

November 22 — FDA Seeks to Change GLPs

November 4 — EMA Releases WFI Q&A

The Parenteral Drug Association presents...

2016 PDA Outsourcing/ CMO Conference

Expanding patient access through collaborative partnerships

November 3-4, 2016 | Washington, DC

Renaissance Washington, DC Hotel

Exhibition: Nov. 3-4 | Courses: Nov. 2

#2016CMO

Conference Theme: *Challenges Facing Outsourcing and Customers: Global Perspectives and Solutions*

The *2016 PDA Outsourcing/CMO Conference* will provide global perspectives on outsourcing, contract manufacturing organizations (CMOs) and integrating the two to achieve product and patient objectives.

This first PDA U.S. Conference on this "hot" industry topic will use an interactive format to explore quality metrics, outsourcing processes and the necessary steps to build strong relationships between clients and CMOs. Expert presenters bring experience and insight on these topics from the perspectives of the client, CMO and the U.S. FDA.

Gain valuable insight for managing a long-lasting and successful partnership for all.

Learn more and register at pda.org/2016CMO.

Preceding the Conference, PDA Education will offer the *2016 PDA Outsourcing/CMO Course Series*. *Technology Transfer* **(Nov. 2)** will cover the business process and technical considerations for technology transfer of large and small molecules; *Establishing a Robust Relationship with Your Client/CMO* **(Nov. 2)** will examine the relationship between CMOs and their clients and offer practical advice on establishing and maintaining effective working relationships.

Take advantage of these unique opportunities to learn more about this important facet of pharmaceutical manufacturing.

Learn more and register at pda.org/2016CMOCourses.

PDA Parenteral Drug Association

PDA's international reputation for quality education and providing the latest advances in the field attracts people from all over the globe to its trusted online resources, conferences and workshops. Reach PDA's actively engaged audience through a multitude of integrated marketing and business development opportunities.

Choose from print and electronic advertising and meeting exhibition and sponsorship opportunities to create a customized package that meets your company's needs! Check out all that we have to offer— and get started soon to capitalize on our full schedule of events and advertising opportunities for 2016. Connecting with "movers and shakers" in the industry is only a phone call away!

Print Advertising in the *PDA Letter*

PDA's premier membership publication is a well-read magazine, published 10 times per year and mailed to nearly 10,000 members and volunteers worldwide. Content from each issue is available online on a newly updated, mobile-friendly website. This new website not only offers enhanced functionality for reading the *PDA Letter*, but also provides our advertisers with additional FREE and paid advertising opportunities.

Go Digital with PDA's numerous Online Advertising Opportunities

Digital advertising is one of the most cost-effective advertising methods as it can increase product awareness and deliver targeted messages to the right group at just the right moment in time. Reach PDA's global audience on the world's most accessible platform – the web.

Digital Advertising Opportunities include:

- Web Ads on PDA.org, Store.pda.org, the *PDA Letter* online and the *Journal of Pharmaceutical Science and Technology*
- Premier advertising placement in PDA's weekly *Connector* eNewsletter
- Online Directories, such as Consulting Services and Supplier Directory and Membership Directory
- PDA's Online Career Center for employers and job seekers

Contact David Hall, Vice President, Sales at (240) 688-4405 or hall@pda.org to learn more and start creating the right advertising package to meet your 2016 business goals.

Health Canada On Track for Drug Shortage Deadline

This summer, Health Canada announced it is on track to meet requirements for reporting drug shortages via a third-party reporting site by its spring 2017 deadline. After the new reporting site is launched, it will replace the current www.drugshortages.ca website. Before the new site is up, however, Health Canada expects companies to continue posting information about drug shortages and product discontinuances on the drugshortages.ca website.

FDA Responds to Zika

In a blog post over the summer, the U.S. FDA announced its plans for minimizing the impact of the Zika virus by partnering with other U.S. government agencies, the private sector and the international regulatory community, including the WHO and ANVISA (the Brazilian Health Regulatory Agency) on vaccines and treatments. As of July, 120 FDA staff members are working in response to the outbreak.

New Pre-RFD Process for Combo Product Submissions

The FDA plans to change its internal procedures for responding to sponsors on preliminary product classification assessments from the Office of Combination Products (OCP). This new process, the Pre-Request for Designation (Pre-RFD) process, will require sponsors to provide a detailed product description. Once OCP receives this information, the Office will make an assessment regarding product classification and Center assignment. The Agency's goal is to respond to sponsors 60 days following receipt of all the necessary information. A draft guidance on this process is forthcoming.

Europe

EMA Reorganizes into Leaner Organization

Beginning Sept. 1, EMA will reduce the number of divisions dealing with human medicines from four to three, create a new function to strengthen collaboration between the Agency and national competent authorities, and streamline the division responsible for administration and corporate management. These changes are expected to result in leaner operations and better administrative support. This reorganization builds on the Agency's 2013–2014 reorganization.

EMA Releases WFI Q&A

EMA has provided a set of draft questions and answers on the production of water for injections by nondistillation methods, i.e., reverse osmosis, to provide preliminary guidance until the ongoing revision of Annex 1 of the GMP guide is complete.

Industry comments on the document are due Nov. 4.

MRHA Guidance Addresses Health Apps

The British regulatory authority MHRA released a guidance in August outlining when certain health apps can be considered medical devices. The guidance features an interactive step-by-step PDF to help developers determine if their product constitutes a medical device. In addition, the guidance offers recommendations for navigating the regulatory pathways for approval. The guidance was developed due to the proliferation of health-related apps available on the marketplace and to clear up confusion.

Asia-Pacific

Indian Regulator to Recruit More Inspectors

India's Central Drug Standards Control Organization (CDSCO) recently announced plans to recruit more than 500 new drug inspectors in 2017 as part of a five-year plan to ensure the quality of drug product manufacturing within India and drug product manufactured for export. In addition, CDSCO hopes to train the recruiters effectively to ensure uniform GMP inspections.

CDSCO recently finished recruiting 147 drug inspectors as part of a push to enhance cGMP inspections of manufacturing units.

International Inspectorate

PIC/S Releases Data Integrity Guide for Inspectors

PIC/S has released a draft data integrity guidance. This draft guidance is being made available to facilitate the effective implementation of data integrity elements into the routine planning and practice of GMP/GDP inspections. The guidance also provides support for risk-based data integrity inspections.

21st Century Manufacturing and Regulation are Here

Inaugural PDA Europe Annual Meeting Sees Future in Injectables

Ursula Busse, PhD, Novartis

We are witnessing a paradigm shift in scientific, technical, and regulatory approaches to healthcare. Innovative technologies raise the quality and safety of our manufacturing and distribution processes and offer increased efficiencies and flexibility. This, in turn, means regulatory oversight is becoming increasingly risk-based as regulators strive for convergence on a global scale. Our industry is evolving toward an increasingly agile and flexible manufacturing mode that can accommodate shifting demands, deliver innovative therapies, and master current and future healthcare challenges. In short, manufacturing in the 21st century will be light years ahead of traditional approaches we have become accostomed to in our daily lives.

On June 28–29, PDA Europe's debut *Annual Meeting* provided first-hand opportunities to learn about new solutions and to hear perspectives from global regulators on these advancements.

The opening plenary session focused on healthcare advancements in the context of globalization and rapid scientific innovation. It covered current approaches to quality management and operational excellence. **Martin VanTrieste,** the current chair of PDA's Board of Directors, mentioned that as disruptive technologies enter the healthcare sector, pharmaceutical companies need to make sure they assume the lead in incorporating these technologies into future treatments. **Jean-Louis Robert,** EMA, presented regulatory considerations and advice to applicants on continuous manufacturing. Finally, insight into the collaboration of regulatory agencies on global scale was provided by **Paul Hargreaves,** current chair of PIC/S.

Wearable Devices, DI Draw Discusssion

Concurrent sessions addressed many of the current challenges industry and regulators face. They featured over 30 presentations with practical examples and case studies. Topics covered included continuous manufacturing, flexible facilities, modern analytical technologies, automation and robotics, blow fill seal technology, Big Data processing and "Industry 4.0," serialization and product tracking implementation, data integrity, innovative injection devices, and—last but not least—regulatory aspects related to all of these.

The data integrity session provided insights into GMP requirements and how companies can understand the dynamics of data integrity breaches. **Anil Sawant,** PhD, Vice President, Quality Management Systems and External Affairs, Merck, relayed the legal aspects of data integrity and covered ongoing initiatives by the PDA Data Integrity Task Force. **Madlene Dole,** Head of Strategic Planning and Operations Group QA, Novartis, presented her company's holistic approach to ensure GxP data integrity.

In the session, "Innovations in Drug Delivery," **Markus Bauss,** Managing Director, SHL Connect, discussed some of the latest innovative drug delivery technologies that lie at the interface of electronics and drug delivery devices. The conversation touched on challenges faced by patients when handling these new technologies along with opportunities, and risks. New biologics therapies under development require higher injection volumes of product with elevated viscosity, resulting in the need for increasinglybetter injection devices. Wearable injectors are being explored for use by oncology ➤

What are the implications of wearable injection devices that connect to your smartphone?

The Parenteral Drug Association presents the...

SAN DIEGO, CA
2016 PDA Data Integrity Workshop

An in-depth, multi-faceted approach to prevention, detection and mitigation of data integrity issues

December 7-8, 2016 | San Diego, CA

Manchester Grand Hyatt

Exhibition: December 7-8 | Courses: December 9

#2016Data

Register by October 24 and save up to $200

The *2016 Data Integrity Workshop* is designed to help companies understand the underlying causes of a major global concern – data integrity problems – and how to resolve them. The final installment of this important Workshop will take place in San Diego, CA, Dec. 7-8.

Gain a broad perspective on common factors involved in data integrity issues, including:

- Quality culture
- Human behavior
- Training needs and technology requirements

Benefit from round table discussions and case studies addressing implementable best practices for preventing, detecting, mitigating and remediating data integrity issues.

Register for the upcoming Workshop in San Diego, CA, and ensure that the data you're reporting is accurate, truthful and complete.

To learn more and register, please visit pda.org/2016DataWest.

Immediately following the Workshop, PDA Education will host the *2016 Data Integrity Workshop Course Series*, which offers two continuing education courses on *Investigating Microbial Data Deviations* and *CMC Regulatory Requirements in Drug Applications*.

To learn more and register for the Course Series, please visit pda.org/2016DataCourses.

patients and devices that communicate data via apps are becoming more and more frequent. Connectivity will also enable outcome-based reimbursement.

Another track featured presentations on global serialization requirements and challenges faced during their implementation at the manufacturing site level. **Michael Ritter,** Novartis, outlined some key success factors to implementation which include: standardization, a lifecycle approach to system maintenance, data integrity, ensuring people skills and capabilities, and deployment using a global governance model. In talking about the European regulatory landscape, **Veronique Davoust,** PharmD, Senior Manager, Global Quality Intelligence, Pfizer, mentioned that a tremendous implementation effort has already been made by companies. The next challenge will be the implementation of the safety feature provisions. Davoust cautioned companies to understand local requirements, incorporate codes for global data standards, consider the impact on artwork changes, and closely monitor progress made. **Akbar Abdollahi,** a regulator from Iran, presented on track and trace implementation in his country and made the link between serialization and Identification of Medicinal Product (IDMP) requirements.

A session on lifecycle management and innovation featured an industry case study covering lifecycle management of vaccines, presented by **Ursula Busse,** PhD, Novartis, on behalf of **Anders Vinther,** PhD, Chief Quality Officer, Sanofi Pasteur. The case study clearly demonstrated the significant impact the current post-approval regulatory landscape has on supply chain complexity and, ultimately, patients. **[Editor's Note:** For more on post-approval changes, see story on p. 34.**]** Recent initiatives put forward by WHO to facilitate post-approval change management for vaccines were presented by WHO's **DianLiang Lei**. The session concluded with discussion on progress made in ongoing work with ICH Q12, *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* and remaining challenges featuring Jean-Louis Robert.

The conference concluded with a look to the future of parenterals, covering products, manufacturing facilities and therapies of the future within a global context. Under the header "Quo vadis, parenteralia?" (Where are you going, parenterals?), **Hanns-Christian Mahler,** Head of Drug Product Services, Lonza, presented on the past and future of injectable dosage forms for biologics. Key takeaways from his presentation were:

- Biologics need to be, and will likely remain, administered parenterally
- The complexity of molecules is increasing and lyophilisates are expected to remain an important dosage form ➤

- The interplay of product design and achieving an adequate Target Product Profile to successful patient treatment is key

- Patient treatment options are evolving and new modalities may question classical requirements and manufacturing approaches

Indeed, subsequent industry speakers **Maik Jornitz,** President, G-Con Manufacturing, and **Morten Munk,** Global Technology Partner, NNE Pharmaplan, made it clear that manufacturing of the future will require more flexible and agile facilities. The biopharmaceutical industry is facing a new reality, where an increased focus on reducing manufacturing costs combines with less predictable market demands for different products in an expanded, increasingly specialized product portfolio. A broad range of tools needs to be activated to meet the requirements for new types of facilities and manufacturing strategies, e.g., a modular approach, single-use technologies, continuous processing and new operational models. **Samvel Azatyan** from WHO, provided insights into the regulatory challenges preventing timely access to most needed new therapies, especially in low- and middle-income countries, and on WHO's role in supporting regulators to address them.

A panel discussion on the future of injectables, with invited panelists from industry, regulatory agencies and international organizations closed the meeting.

Opportunities to interact with speakers, industry peers, regulators, exhibitors and PDA leadership were plenty. They include extended networking breaks, a networking reception on the evening of June 28 and an extremely well attended breakfast for new PDA members. Interactive roundtable discussions with PDA chapter representatives from Italy, France, the United Kingdom, Israel and Japan provided opportunity to connect to an international audience and worldwide PDA membership.

About the Author

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

Susan Schniepp, Regulatory Compliance Associates Inc.

PDA Offers Tools for Ensuring Good CMO Relationships

Each year, demand for pharmaceutical outsourcing increases. More and more companies are moving operations offsite and partnering with contract manufacturing organizations (CMOs). But this shift is bringing new challenges to the industry. How can companies maintain good relationships with their outsourcing partners while also holding them accountable for adhering to their quality standards?

PDA has recognized this pressing challenge for a while now. In 2012, the Management of Outsourced Operations Interest Group held its first meeting at the *2012 PDA/FDA Joint Regulatory Conference*. This group continues to meet and has recently participated in combined interest group meetings with the Supply Chain Management and Pharmacopeial Interest Groups. The group also has an active forum on PDA Connect℠ (community.pda.org).

In 2013, PDA also published the book, *Pharmaceutical Outsourcing: Quality Management and Project Delivery*. Chapters within this book cover legalities of contract manufacturing, benefits and pitfalls of outsourcing IT services, quality management systems, etc. **[Editor's Note:** The infographic on p. 32 uses material from the chapter on auditing.**]**

In addition to these activities, PDA is also proud to announce it is holding its first U.S.-based conference devoted to contract manufacturing and outsourced operations this November in Washington, D.C. The conference planning committee has put together a program that is designed to discuss some of the most important and impactful issues facing the industry today from the perspective of the U.S. FDA, outsourcing operations and their clients.

The conference will kick off with a session where representatives from FDA and industry will explore quality metrics. With the advent of reporting quality metrics to the FDA, the planning committee wanted to understand how CMO's will adapt to sharing their information both with customers and with the Agency, and ramifications of their changes to communication strategies with clients. Conference attendees will also hear about how to identify and select CMOs as well as the importance of the Quality Agreement and how implementing an effective agreement leads to increased product quality and safety.

In addition to this conference, PDA Europe will hold its *Outsourcing & Contract Manufacturing Conference* in mid-November in Barcelona. This follows a series of successful European conferences on outsourcing offered since 2014.

While there are challenges to building a successful relationship between the contracting organization and the CMO, PDA has a wealth of resources to help both parties achieve success.

Where do leading experts turn to communicate with the PDA community?

The *PDA Letter* and *PDA Journal of Pharmaceutical Science and Technology*

You can too!
Authors wanted

For more information on PDA publishing please visit:

www.pda.org/pdaletter **http://journal.pda.org**

Lights, Camera, Action!

It has been about a year since the *PDA Letter* jumped into the editorial video business. While there was nothing groundbreaking in the world of publishing about introducing video "articles," it was a big move for the already overtaxed Letter staff—all three of us. In light of trends, however, we felt it was important to add this storytelling medium to our lineup. After all, there is a whole generation growing up right now who religiously follow their favorite "YouTubers" on their personal smartphones. So the Letter had to take that leap.

While our videos are low-budget productions, the team is spending a great deal of time constructing these "stories." In fact, we carved out a "multimedia" subgroup of the *PDA Letter* Editorial Committee who help us identify experts to interview, develop questions, and scrutinize scripts.

So far, the videos have been successful by many measures. First and foremost, they are being viewed! We've produced six videos so far and have had over a thousand views. The average time spent on our videos is more then three minutes, which is great since most of the videos are shorter than that.

So far, our participating experts have enjoyed the experience. We've filmed members of the PDA Data Integrity Task Force, Merck's Manufacturing CIO, and PDA's current Chair on topics of great importance to the members. At last week's *PDA/FDA Joint Regulatory Conference,* we filmed two video articles, one on the impact of achieving a breakthrough therapy designation on manufacturing and quality and another on PDA's Post Approval Change Innovation for Access to Medicines (PAC iAM℠) Task Force activities. These are in production now and will be posted soon.

We aren't doing anything fancy. *60 Minutes, BBC* or *France24* we are not!

Although our equipment is basic (an iPad mini, a $200.00 microphone, three shop lights, diffusion paper, four tripods) and we appear more like a high school video club team than professional videographers, our subject matter experts continue to take our production very seriously. And they should! We collectively work on scripts to ensure we deliver meaningful stories within two or three minutes. The Letter staff seeks out suitable filming locations that can be lit adequately and allow good sound quality.

We took time to develop a name for the *PDA Letter* videos ("On the Issue") and purchased music for the opening and closing of each edition. Recently, we began splurging on "b-roll" videos to make the productions more visually interesting! In the future, I anticipate upgrading some of the equipment as well as the software we use to produce the final videos.

Of course, all that depends on if people watch. I encourage you to go to the multimedia section of www.pda.org/pdaletter and see what you think, if you haven't already. Then give us your thoughts. If you have a suggestion about subjects or subject matter experts you'd like to see, we want that information, too! Who knows, maybe you'll be the next person who hears, "Lights, Camera, Action!"

PDA Letter

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

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

Subscriptions are not available.
Articles in the PDA Letter may be reproduced with permission—
contact the PDA Letter Editor for details. © *PDA 2016*

PDA Letter Staff

Walter Morris
PDA Letter Editor,
Senior Director of Publishing
+1 (301) 656-5900, ext. 148
morris@pda.org

Rebecca Stauffer
Assistant Editor
stauffer@pda.org

Katja Yount
Publication Design Specialist
yount@pda.org

PDA Letter Editorial Committee

Maria Brown, *Celgene*
Winston Brown, *Phillips-Medsize*
Anne Connors, *EMD Millipore*
Robert Darius
Michael De Felippis, Ph.D., *Eli Lilly*
Mirko Gabriele, *Patheon*
Sy Gebrekidan, *Merck*
Chris Hanff, *Concordia ValSource*
Maik Jornitz, *G-Con*
Robert Lechich, *Pfizer*
Edwin Rivera Martinez, *Sanofi*
Youwen Pan, *Roche/Genentech*
Pritesh Patel, *Novartis*
Praveen Prasanna, PhD, *Shire*
Cecilia Turoff, *Baxter Healthcare*
Tricia Vail, *Pall Life Sciences*
Ilana Zigelman, *Orgenics*

To Advertise, Contact

Dave Hall, Vice President, Sales
+1 (301) 656-5900 ext. 160
hall@pda.org

PDA Global Headquarters — Bethesda Towers

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

PDA Europe — Am Borsigturm 60

13507 Berlin, Germany
Tel: 49 30 4365508-0 Fax: +49 30 4365508-66
petzholdt@pda.org

PDA Training & Research Institute

4350 East West Hwy., Suite 600
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900 Fax: +1 (240) 482-1659
info-tri@pda.org

The *PDA Letter* Podcast Series

Listen to leading experts on LAL, biosimilars, the future of manufacturing, and more!

In our Podcast Archive, you can listen to the following experts:

- Hospira's Sumant Ramachandra
- Sandoz's Joerg Windisch
- Dr. Jack Levin, co-discoverer of the groundbreaking LAL test
- Lonza's Allen Burgenson
- Amgen's Madhu Balachandran
- Pfizer's Michael O'Brien

For more information on all PDA podcasts and other interviews please visit:

www.pda.org/pdaletter

Vitek MS™

KNOWLEDGE BASE EXPANSION WITH ADDITIONAL ENVIRONMENTAL MOULDS, YEAST AND BACTERIA

FROM THE INVENTOR OF AUTOMATED IDENTIFICATION

Comprehensive identification expertise

www.biomerieux.com

BIOMÉRIEUX INDUSTRY

PIONEERING DIAGNOSTICS