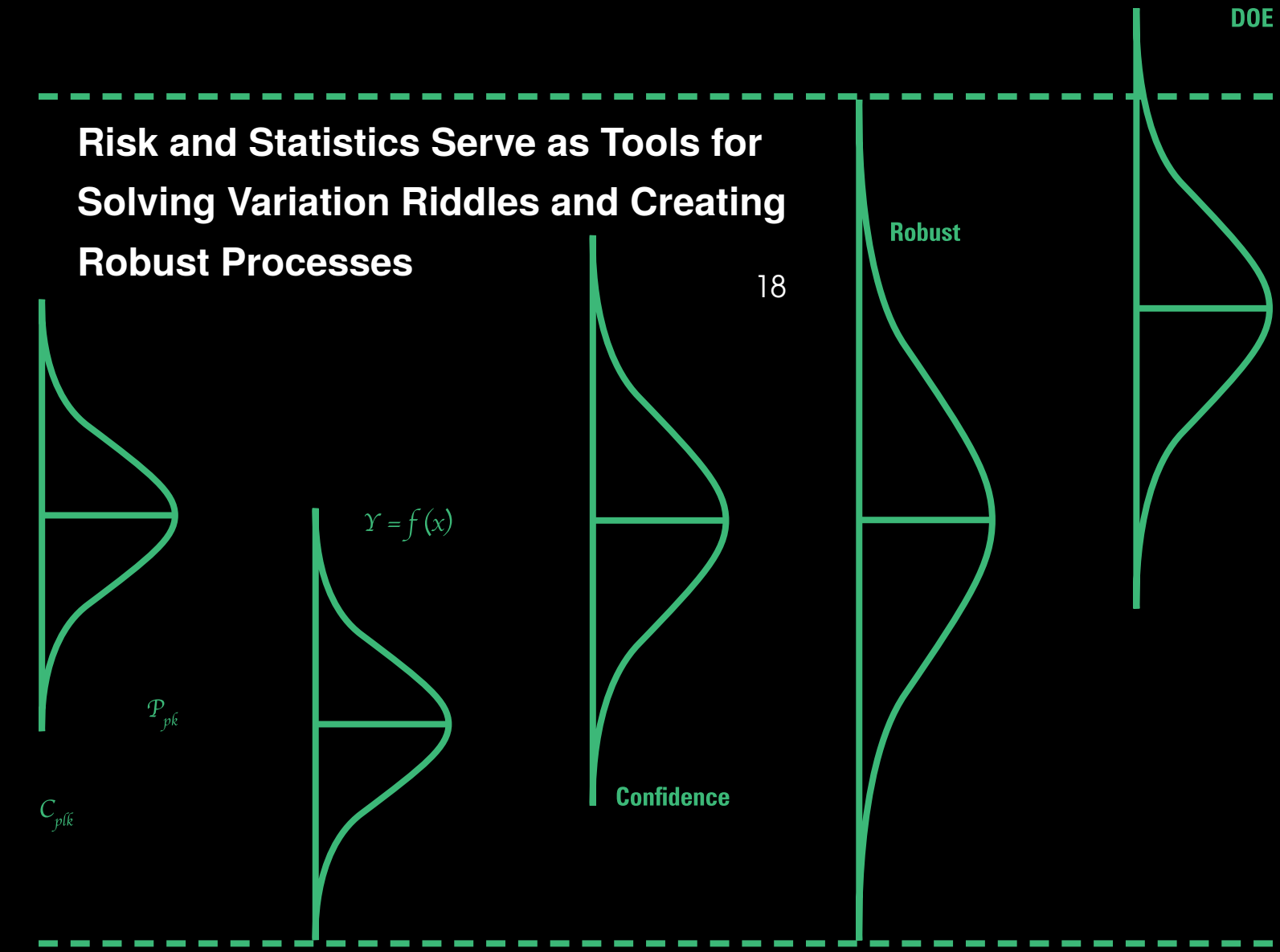
People • Science • Regulation

PDA Letter

Volume XLIX • Issue 4 www.pda.org/pdaletter April 2013

Risk and Statistics Serve as Tools for Solving Variation Riddles and Creating Robust Processes

18



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The *2013 PDA/FDA Joint Regulatory Conference* – a signature PDA event – will facilitate speakers from both regulatory authorities and industry to clearly explain proposed and finalized requirements along with current "best practices."

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2) **Innovation and Technology**
3) **Integrated Approach to Product Life Cycle.**

These tracks are designed to inform, educate and stimulate the participant's mind by connecting regulations with practical approaches to current best practices on a variety of topics. The knowledge gained at this conference will be invaluable in helping attendees establish a holistic approach for managing their company's product lifecycle with a compliant but practical program.

Hear directly from FDA experts, decision makers as well as industry professionals who are willing to share their insights and experience.

Visit **www.pda.org/pdafda2013** for more information and to register.

Exhibition: September 16-17 | Workshop: September 18-19 | Courses: September 19-20

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JUNE 2013

Aseptic Processing Training Program
Bethesda, Maryland
www.pda.org/2013aseptic

- Session 3: June 3-7 and June 24-28, 2013 SOLD OUT
- Session 4: August 26-30 and September 23-27, 2013
- Session 5: October 14-18 and November 4-8, 2013

PDA/FDA Pharmaceutical Supply Chain Workshop Course Series
June 6 | Bethesda, Maryland
www.pda.org/supplychaincourses2013

- Risk Management for Temperature Controlled Distribution – New Course
- Active Temperature Control Systems: Qualification Guidance – New Course

Fundamentals of Aseptic Processing
Bethesda, Maryland
www.pda.org/apfundamentals

- Session 1: June 10-14
- Session 2: December 16-20

PDA Aseptic Processing-Sterilization Conference Course Series
June 18-19 | Chicago, Illinois
www.pda.org/asepticsterilizationcourses

- Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Validation and Ongoing Control (June 18)
- Parametric Release of Pharmaceutical and Medical Device Products Sterilized with Moist Heat (June 19)
- Validation of Dry Heat Processes (June 19)

JULY 2013

Fundamentals of an Environmental Monitoring Program
July 23-24 | Bethesda, Maryland
www.pda.org/environmental2013

PDA TRI Filtration Week
July 29-August 2 | Bethesda, Maryland
www.pda.org/filtrationweek2013

- Filters and Filtration in the Biopharmaceutical Industry – Basics Course (July 29-30)
- Filters and Filtration in the Biopharmaceutical Industry – Advanced Course (July 31-August 2)

For more information on these and other upcoming PDA TRI courses, please visit www.pda.org/courses

Laboratory Courses

The PDA Training and Research Institute is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education.

PDA Letter

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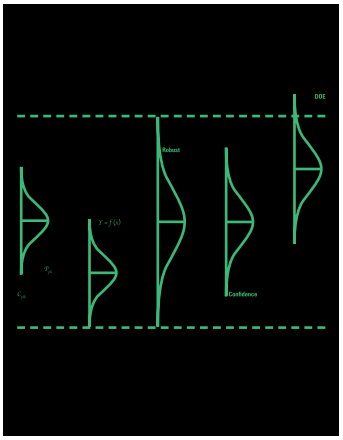
Cover



Cover Art Illustrated by Katja Yount

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TRI — Education

Voices of PDA

Contents

Features

Nominate Your PDA Peers for the Board of Directors

PDA's Board of Directors wants to continue membership involvement in the selection of PDA leadership with the open nomination process for Board of Directors, which was adopted for the first time last year.

Previously, the nominating committee (comprised of the members of the Executive Committee) nominated long-term active PDA members for the elections to the BoD. Based on the success of the open nomination process last year, we would like to extend the nomination process once again to the entire PDA membership. The open nomination process ensures that the BoD is truly representative of PDA's increasingly diverse and international membership.

"We do not want to miss outstanding members of our organization and strive for having a multifaceted Board of Directors," Maik Jornitz, the current Nominating Committee Chair and Immediate Past Chair of PDA, points out.

All PDA members are encouraged to nominate their peers within the Association for the Board of Directors election, although certain prerequisites are necessary. For example, only members in good standing can nominate and be nominated (that is, their membership is current).

The PDA Nominating Committee will consider all nominations and base their selection upon the following criteria: 1) status of membership; 2) level of activity within PDA; 3) volunteer history; and 4) length of membership.

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

To nominate, send an email to: nominate@pda.org. Nominations for the 2013 BoD elections will be accepted through June 14, 2013.

Process Validation Technical Report Now Available

Josh Eaton, PDA

The long-awaited publication of PDA's technical report on process validation has arrived! *TR 60: Process Validation: A Lifecycle Approach* details the three stages of process validation: process design, process qualification and continued process verification. The preliminary efforts were undertaken by a diverse group of subject-matter experts who provided input and perspective from companies and regulatory bodies in the United States and Europe. From this large amount of contributed material and insight, a small team of industry experts worked over the last several months to coalesce the information into its final form.

Through continued input from the team at-large, as well as an extensive and valuable review by U.S. FDA representatives, the finished product presents a comprehensive view of process validation theory and methodology. The report comprehensively presents material covering process controls and parameters, process performance qualification (PPQ) and methods for continuous process verification. Additionally, the technical report also presents the use of enabling tools such as process analytical technology (PAT), quality risk management (QRM), technology transfer and knowledge management as they relate to process validation.

Readers of TR60 will also have an opportunity to expand upon the knowledge provided in the technical report by taking advantage of the upcoming *2013 PDA/FDA Process Validation Workshop* scheduled for May 20-21 (see story on p. 36). At this workshop, attendees will interact with leading experts and get a first-hand perspective on the latest issues, problems and future viewpoints regarding process validation. Some of the topics include FDA's new process validation guidance, case studies, and the use of statistics in process validation.

To purchase a copy of the report go to store.pda.org/ProductCatalog/Product.aspx?ID=1931

Three Reg Speakers Confirmed for Process Val Workshop

PDA is pleased to announce that three high-level regulators from the United States and Europe will speak at the *2013 PDA/FDA Process Validation Workshop*, May 20–21 at the Hyatt Regency in Bethesda, Md. They are:

- **Jeffrey Baker,** PhD, Deputy Director, Office of Biotechnology, CDER, U.S. FDA
- **Lina Ertle,** Quality Assessor, ANSM (France)
- **Patrick Swann,** PhD, Deputy Director, Division of Monoclonal Antibodies, CDER, FDA

"With global regulatory expectations for process control and validation changing in recent years, PDA's members recognize the importance of engaging health authority representatives at a workshop like this," said **Richard Johnson,** PDA President and CEO. "PDA has a long history of providing forums for manufacturers to exchange the latest thinking with their regulatory counterparts, and it is common for representatives of health authorities from different countries to appear at our meetings to open dialogue with industry experts."

The workshop is intended to help industry learn about the U.S. and European regulatory perspectives on process validation. In recent years, regulators have expected manufacturers to take a life-cycle approach to process validation and utilize risk-management and statistical tools. Process validation experts from industry, representing companies like Pfizer, Baxter Healthcare and Amgen, also will present. For more information about the event, see story on p. 36.

PDA Volunteer Spotlight

Edward Balkovic, PhD

- Principal Microbiologist – Contamination Control
- *Genzyme – a Sanofi company*
- Member Since | April 1994
- Current City | Milford, MA
- Originally From | Irvington, NJ

Ed's sixth-grade science teacher sparked his interest in biology.

I have always been able to return to my job with new knowledge.

What is an issue or trend in your industry you think more people should be talking about?

We should be discussing the concept that "Good Science" is "Good cGMP Compliance," especially in my area of quality operations. I think too many companies are mistakenly cutting back on supporting "Good Science" in this area, and it is leading to numerous compliance issues with the regulatory agencies.

What lessons has your work life taught you?

Always construct your opinions after a thorough review and analysis of the appropriate data, with the understanding that your opinion can change if the data changes.

If you could live in any other time in history, when would it be?

Since I am a history buff, I would have liked to have lived during the U.S. Civil War.

When you were a child, what did you want to be when you grew up?

I wanted to be a scientist, specifically a marine biologist. Now as a microbiologist, I have realized my vision, beginning as a Clinical Virologist at the National Virology Reference Lab for all Veterans Affairs medical centers and then onto the vaccines/biotech industries as a Quality Control Microbiologist.

What have you gained by being a PDA volunteer?

Volunteering on PDA task forces and conference planning committees has provided me with numerous opportunities to meet and network with distinguished experts from both our industry and regulatory agencies. I have always been able to return to my job with new knowledge and a better understanding of the major issues affecting our industry.

What is your favorite thing about being a PDA member?

Being able to meet, converse and network with industry and regulatory colleagues/experts.

To volunteer with PDA, visit www.pda.org/member-volunteer

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chapter update

PDA Metro Chapter Learns the Fine Art of Investigations

PDA Metro Chapter President Lara Soltis, Texwipe

On February 6, the PDA Metro Chapter hosted a dinner meeting at the Holiday Inn in Somerset, N.J. **Randy Hutt,** PhD, an independent consultant with an expansive knowledge of the pharmaceutical industry in the greater New York metropolitan area, presented the talk, "Microbiology Investigations in Aseptic Processing." There were 40 attendees including PDA Metro Chapter officers and a sampling of microbiologists and compliance officers from local pharma companies, such as: J&J, Genzyme/Sanofi, Merck, Celgene and Medtronic. EMSL Analytical from Cinnaminson, N.J., sponsored the event and showcased their full-service analytical laboratory that is U.S. FDA-registered, CGMP-compliant, DEA-licensed and ISO 17025-accredited.

For 45 minutes, a rapt audience listened to Hutt, who presented case studies based on actual experiences that she cleverly dubbed "War Stories" so that we, the listeners, could learn from others' mistakes. She broke down aseptic processing investigations into the following areas: sterility test failures, environmental and personnel monitoring excursions and process simulations of aseptic media fills. Investigation templates were provided that we have also made available on our website. The form allows for the investigator to document "gut feelings" on the possible root cause, as microbiology is often more of an art than science. Plus, more often than not, there's no definitive root cause discovered, only "most probable root causes" such that it's recommended to conclude your investigation with the statement that "the most probable root cause is…"

Some other key thoughts conveyed by Hutt: your employees are your best assets in pharma, especially people with differing opinions than yourself; involve engineers, microbiologists, pharmacists, etc., in investigations to offer another set of eyes; and ask if anything changed in a process or if anything was added or "improved."

During the Q&A that followed, **Jim Agalloco** expanded on a question from the audience and explained that data trends may be difficult to capture mathematically as most results will be 0 cfu. There is essentially no difference between 1 and 2 cfu, however, if you always see 0 and now you have three incidences of 2 cfu in a row – even though it's less than your alert/action limit – your instinct may tell you it's a trend, and therefore, it should be investigated.

After the presentation, the chapter conducted a raffle. The winner was **Kaitlin Tilney,** Specialist of Clinical Production at Celgene Cellular Therapeutics in Warren, N.J., who won a free year of membership to PDA!

After closing remarks informing attendees of our upcoming all-day "Chapter Day" on April 10 centered on the theme of process validation, the full room dispersed and the PDA Metro Chapter volunteers said goodnight.

(l-r) Jim Agalloco, Agalloco & Associates, (past Chapter President and past PDA President), Lara Soltis, Texwipe (Chapter President), Leticia Quinones, Bristol-Myers Squibb (Chapter President-Elect), Bob Johnson, PSC Biotech (Immediate Past President), and Randy Hutt, PhD, San-Mar Laboratories, Inc. (Speaker)

Much thanks to Jim Agalloco of Agalloco & Associates who chaired this meeting; **Bob Johnson** of PSC Biotech, PDA Metro Chapter Immediate Past-President; **Mary Ly Huynh,** PDA Metro Chapter Treasurer; **Leticia Quinones,** PhD, Bristol-Myers Squibb, PDA Metro Chapter President Elect; **Maggie Filipowicz,** Laureate Biopharma, PDA Metro Secretary; **Simon Laufler,** Laureate Biopharma, and myself, Lara Soltis, Texwipe, PDA Metro Chapter President.

The Metro Chapter is a very active chapter with current upcoming dinner seminars, full-day courses, FDA Speakers and networking opportunities. For more information on upcoming meetings please see the PDA Metro Chapter home page from www.pda.org.

PDA Parenteral Drug Association

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5 Reasons You Need to Be on LinkedIn Even When You Have a Job

Joshua Waldman, author of *Job Searching with Social Media For Dummies*

A question I frequently get when training job seekers on using social media is "Won't my boss think I'm looking for another job if I'm using LinkedIn?"

With over 180 million LinkedIn users in the world, I honestly don't think that even half of them are actively seeking work. More than likely, they are happily employed and happily networking. It is a mistake to think of LinkedIn as a giant job board and your profile as just another résumé. The power of any social networking tool is in the networking.

So, if you are currently employed and not taking your LinkedIn use seriously, you're making a grave error. Here are five reasons:

1 You need to have a large network so you can use it later

Imagine you just got laid off. And you have then people in your LinkedIn network. You suddenly realize that you should have invested more in getting to know people. So you start to add people like crazy to your network.

If LinkedIn doesn't blacklist you for suspicious behavior, then the droves of new people you are inviting to your network will question your intentions. They might think, "I haven't heard from this guy in ten years, now all of a sudden he's lost his job and wants to connect. What does he want from me?"

It's always better to dig your well before you need to drink from it. If you haven't been building social equity with your network, you'll have little to draw from later. So don't wait until you need it. Build a strong network on LinkedIn now. Be active. Provide value. Stay in touch.

2 Opportunities come to you; recruiters look for passive candidates

When a company hires a contract recruiter to fill a job requisition, that company isn't looking for someone unemployed. They wouldn't need to hire a contract recruiter for that. There are enough unemployed people to fill every single job vacancy in the country. What the organization needs is someone who is not actively looking, called a passive candidate.

In other words, the recruiter is paid to headhunt, steal and pillage from competitive companies, convince the happily employed person that the grass is greener, and get a huge commission from the new hire. Companies who use headhunters are willing to pay you more than what you are making now in order to snatch you away from your cushy job.

If you aren't on LinkedIn, you are reducing your chances of being discovered by headhunters and having the opportunity to make more money.

3 Industry groups can offer you value and connection

Groups on LinkedIn have really matured. I've found that the discussions on groups are more engaging, people are less shy about speaking their minds and the content is improving in quality. Of course this depends on the group; this is just from my own experience. However, if you find the right groups to participate with, the value to your network and knowledge is huge.

Not only will you be exposed to news, and new ideas, but you'll have a chance to demonstrate your expertise through commenting and discussion. Sometime alliances are formed.

For example, I was part of a group whose leader would entice you to click links to download some attractive research reports. But in order to download each report, you had to fill out a lot of personal information. I found this practice annoying and said so. Pretty soon, oth-

ers in the group were agreeing with me. One guy in particular contacted me and we hit it off. Turns out we do similar things, but on separate continents. Thus both of our networks grew stronger.

4 Keep your résumé up to date just in case

A résumé is a static thing. You write it once when you are actively looking for work. You get your job. Then you forget about it.

LinkedIn profiles tend to stay up to date with greater accuracy than any other online profile. Recruiters know this. They know that your profile will be more accurate than your five-year-old résumé.

When you keep your profile up to date, writing your new résumé will be that much easier. Instead of staring at a blank piece of paper trying to remember your start and stop dates, you'll just check your profile and know.

Look, you never know when you'll need a résumé. Most employment these days is at-will. Your company doesn't need any reason to let you know tomorrow. Be ready.

5 Read the news feed for your industry

The average time spent on LinkedIn is just over four minutes per visit. The company finds this dismal fact upsetting, and does what it can to keep you on. And some of the ways it does that are actually quite good. With LinkedIn Today, you get customized news delivered to you daily. Based on your industry, the types of articles you share, and who is in your network, your daily news feed is likely going to inform you of things you should know about your job.

On many occasions, I've found trending news items that I was blind to until I saw them on LinkedIn. You can customize how your news is displayed and what categories you are interested in reading about. My favorite is the ability to see what news items are trending in my own network. I'd like to know what my peers are reading. Wouldn't you?

About the Author

Joshua Waldman is an authority on leveraging social media to find employment. He is the author of *Job Searching with Social Media For Dummies,* and his writing has appeared in *Forbes, Mashable* and *The International Business Times.* Joshua's career blog, CareerEnlightenment.com, has helped thousands of readers each month get ahead using his job advice. Joshua is also speaker and trainer who specializes in helping job seekers gain control of their careers in today's competitive economic and technology climate. He presents keynotes, trainings and breakout sessions around the country for students, career advisors, consortiums and professional organizations. For more information about his speaking, visit careerenlightenment.com/speaking.

snapshot

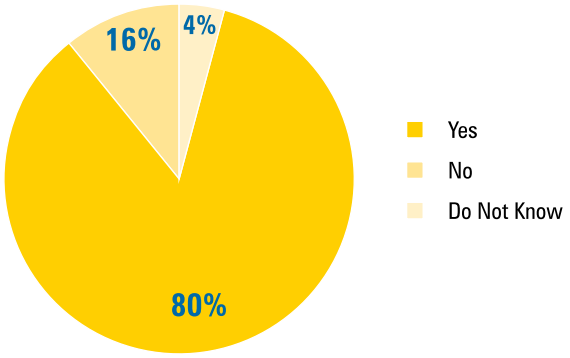
In*Print*

PDA Survey: Business Case for Pharmaceutical Quality

The inaugural book in the "PDA Survey" series addresses the business case for pharmaceutical quality. This 2011 PDA benchmarking survey examines the cost of poor quality and the essential role of good quality systems in the pharmaceutical industry. Questions 92-95 (reproduced here) are related to the role of the quality system.

Question 92 (45 Respondents): *Do you have a preventive process in place to continuously invest in process improvements, operator retraining, etc., to achieve continuous improvement on the quality of product produced?*

Answer Options	Response Percent	Response Count
Yes	80.0%	36
No	15.6%	7
Do Not Know	4.4%	2

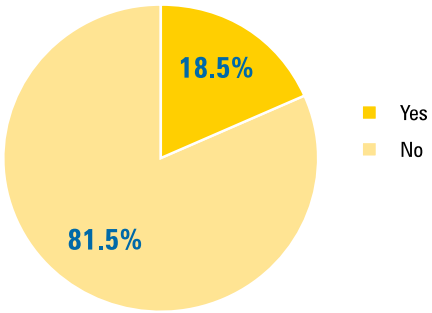


Question 93 (27 Respondents): *Is the return on quality model linked to your quality system elements? If yes, which elements?*

Answer Options	Response Percent	Response Count
Yes	18.5%	5
No	81.5%	22

If Yes, please indicate the elements:

- Organization effectiveness (2)
- Unspecified (2)
- Return on quality is used in remediation plans and product assessments, chosen based on turnover of product, lost sales + profits if no plans are implemented (1)



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Journal *Preview*

March/April Issue Covers Hot Topics

The March/April issue includes contributions by a number of authors from the U.S. FDA. **Richard Friedman, Dennis Guilfoyle, Patricia Hughes, David Hussong** and **Amy Rosenberg** write about the microbial risk in pharmaceutical manufacturing and the link to ICH Q9. **Kurt Brorson** is a coauthor on two Meeting Reports from the *2012 PDA Virus and TSE Safety Forum.* The issue also includes six research papers on various important topics

Conference Report

Hannelore Willkommen, et al., "Meeting Report: PDA Virus and TSE Safety Forum"

Hannelore Willkommen, et al., "Meeting Report—Workshop on Virus Removal by Filtration: Trends and New Developments"

Research

Nader Shafiei, et al., "Transformation in the Pharmaceutical Industry—A Systematic Review of the Literature"

Matthew Hammond, et al., "Identification of a Leachable Compound Detrimental to Cell Growth in Single-Use Bioprocess Containers"

Farzin Hadizadeh, et al., "Sustained Delivery of Amphotericin B and Vancomycin Hydrochloride by an Injectable Thermogelling Tri-Block Copolymer"

Mangesh Bhalekar, et al., "Formulation and Optimisation of Sustained Release Spray-Dried Microspheres of Glipizide Using Natural Polysaccharide"

Harry Yang, "Establishing Acceptable Limits of Residual DNA"

Purvi A. Shah, et al., Cleaning Validation: Quantitative Estimation of Atorvastatin in Production Area

Bipul Nath, et al., "Studies on Stercuia Gum Formulations in the Form of Osmotic Core Tablet for Colon-Specific Drug Delivery of Azathioprine"

Editorial

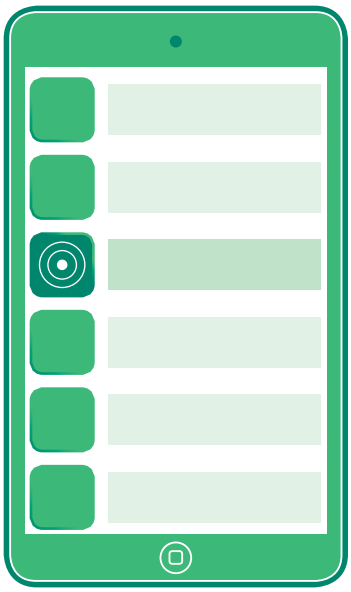
Kurt Brorson, et al., "Microbial Risk in Pharmaceutical Manufacturing and ICH Q9"

Tech *Trends*

ACS Roundtable Develops App for Greener Pharma

Rebecca Stauffer, PDA

What if there was a tool that allowed you to reduce waste during the drug development process? What if there was a guide for identifying potentially environmentally-friendly alternatives to harmful solvents? Fortunately, there is such a guide; in January, the American Chemical Society announced that the organization's Green Chemistry Institute Pharmaceutical Roundtable (which includes representatives from Pfizer, J&J, Merck, Eli Lilly, and others) had developed a mobile app for Apple and Android devices that provides an overview of 60 different types of solvents, their chemical and physical properties, as well as environmental ratings for each solvent.



In an article in *ACS Sustainable Chemistry & Engineering*, scientists **Sean Ekins,** PhD, **Alex M. Clark,** PhD, and **Antony J. Williams,** PhD, discussed the need for such an application in the development of medicines ***(1).*** They noted that traditional processes generate 25-100 times more waste than the chemical under development, and encouraged pharmaceutical manufacturing staff to use the mobile app as a tool for reducing such waste. Going further, they defined "green chemistry" as "The utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products."

Founded in 2005, ACS' Green Chemistry Institute Pharmaceutical Roundtable comprises representatives of 14 pharmaceutical companies. The group is tasked with encouraging innovative technologies in green chemistry and engineering within the pharmaceutical sector. Other initiatives involve integrating information about green chemistry in electronic laboratory notebooks, using process mass intensity to drive sustainable processes and implementing solvent-less reactor cleaning.

Reference

1. Ekins, S., Clark, A.M., and Williams, A.J. 2013. Incorporating Green Chemistry Concepts into Mobile Chemistry Applications and Their Potential Uses. *ACS Sustainable Chemistry & Engineering* 1: 8-13. pubs.acs.org/doi/abs/10.1021/sc3000509.

AB *Report*

BioAB Keeps Pace With Emerging Biotech Trends

Rebecca Stauffer, PDA

PDA's Biotechnology Advisory Board (BioAB) is currently working on a number of exciting projects. The *PDA Letter* spoke with the chair of the BioAB, **E.J. Brandreth,** SVP, Quality and Regulatory Affairs, Althea Technologies.

"We've got a talented group of industry experts, including great FDA representatives and we're focusing on the latest topics in biotechnology," he said. One area where the group is looking to expand is in gene and cell therapies.

"Within the past four or five years there has been resurgence in gene- and cell-based therapies," Brandreth indicated, stating that the BioAB is expanding its activities in this area.

"We're also looking at single-use systems," he said. "The biotech industry has transformed over the past decade with the use of single-use systems. So, instead of buying a big expensive stainless steel tank, you can buy a much less expensive plastic bag, use it once and throw it away. You don't have to worry

Continued at top of page 17

Journal *POV*

The *PDA Journal* – at the Confluence of Academia, Government, and Industry

Govind Rao, PhD, Journal Editor

Recently our profession has been rocked by the senseless deaths of several dozen patients, with hundreds more sickened by contaminated steroid injections. The incident is still under investigation, but it will certainly alter the regulatory landscape for the future. Such a devastating incident underscores the need for advancing regulatory sciences and a strong collaborative relationship between academia, government, and industry.

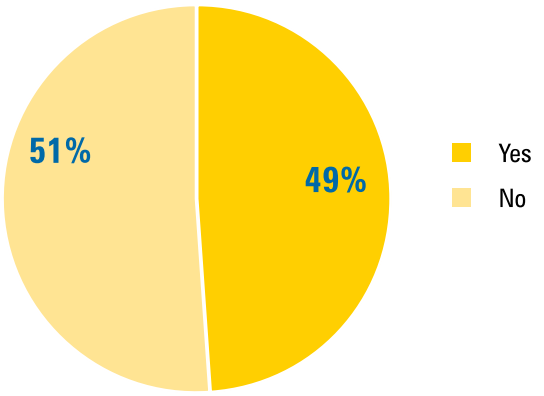
The *PDA Journal* is right at such a confluence, and we will continue to provide scientific leadership by publishing the highest quality articles. In this context, we are delighted to welcome **Beth Junker,** PhD, as the newest member of our editorial team. She is a highly accomplished industry professional. Her experience with a broad array of pharmaceutical product development and regulatory aspects makes her an ideal complement to the current team. We eagerly look forward to her insights and contributions as we continue to move the *Journal* forward in its mission of connecting people, science, and regulation. Details of her many accomplishments are in her biographical sketch on the editorial page (journal.pda.org/site/misc/edboard.xhtml). Please join us in welcoming her, and start sending her your articles!

snapshot

In Print continued from page 14

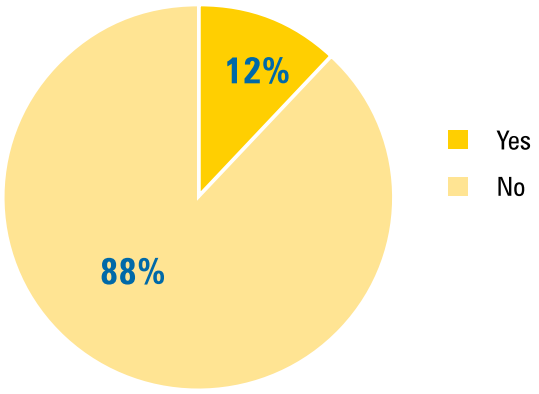
Question 94 (33 Respondents): *Has your company seen a reduction in deviation and investigation rate as a consequence of implementing ICH Q8-10?*

Answer Options	Response Percent	Response Count
Yes	51.5%	17
No	48.5%	16



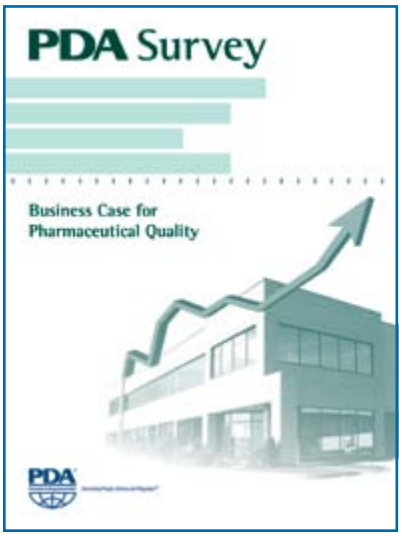
Question 95 (33 Respondents): *Have you incurred health authority sanction costs due to manufacturing deficiencies?*

Answer Options	Response Percent	Response Count
Yes	12.1%	4
No	87.9%	29



[Question 95 Continued] If yes to above, for each cost category below, what is the magnitude of these costs over the past five years? Select all that apply.

Answer Options	Less than $1M	$1M to $10M	$11M to $100M	More than $100M	Response Count
Fines or penalties	3	0	1	0	4
Delayed product launch or approval	2	1	1	0	4
Import bans	2	0	2	0	4
Loss of product or establishment license	2	1	1	1	5
Disgorgements	2	0	0	1	3
Consent Decrees	1	0	0	1	2
Shareholder(s) lawsuits	1	0	1	0	2
Loss of market share	0	1	1	0	2
Recalls due to regulatory scrutiny	1	2	1	0	4



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AB Report continued from page 15

about cleaning it, cross-contamination or sterilization issues, and that has saved the industry millions and millions of dollars. So we've got a technical report coming up on single-use systems that we're working on."

Brandreth considers the group's most "significant and cutting edge" project its work on analytical methods.

"We've got a great deal of work going on for analytical methods for virus detection and control," he said. "**Kathryn King** and **Mike Wiebe** are working on several complex projects on both advanced and emerging methods of viral detection, and the control strategies for virus contamination, including prevention, mitigation and response. It's addressing a problem that causes literally hundreds of millions of dollars of loss each year." (Please note that PDA is hosting a workshop on analytical methods development and validation in October. See www.pda.org/amd2013 for more details.)

Other BioAB current topics of interest include mycoplasma contamination, biofilm and the reprocessing of biopharmaceuticals.

Brandreth urges PDA members interested in biotechnology issues to consider joining one of the BioAB's interest groups.

"The interest groups are always receptive to volunteers," he emphasized. "We always welcome new subject matter experts."

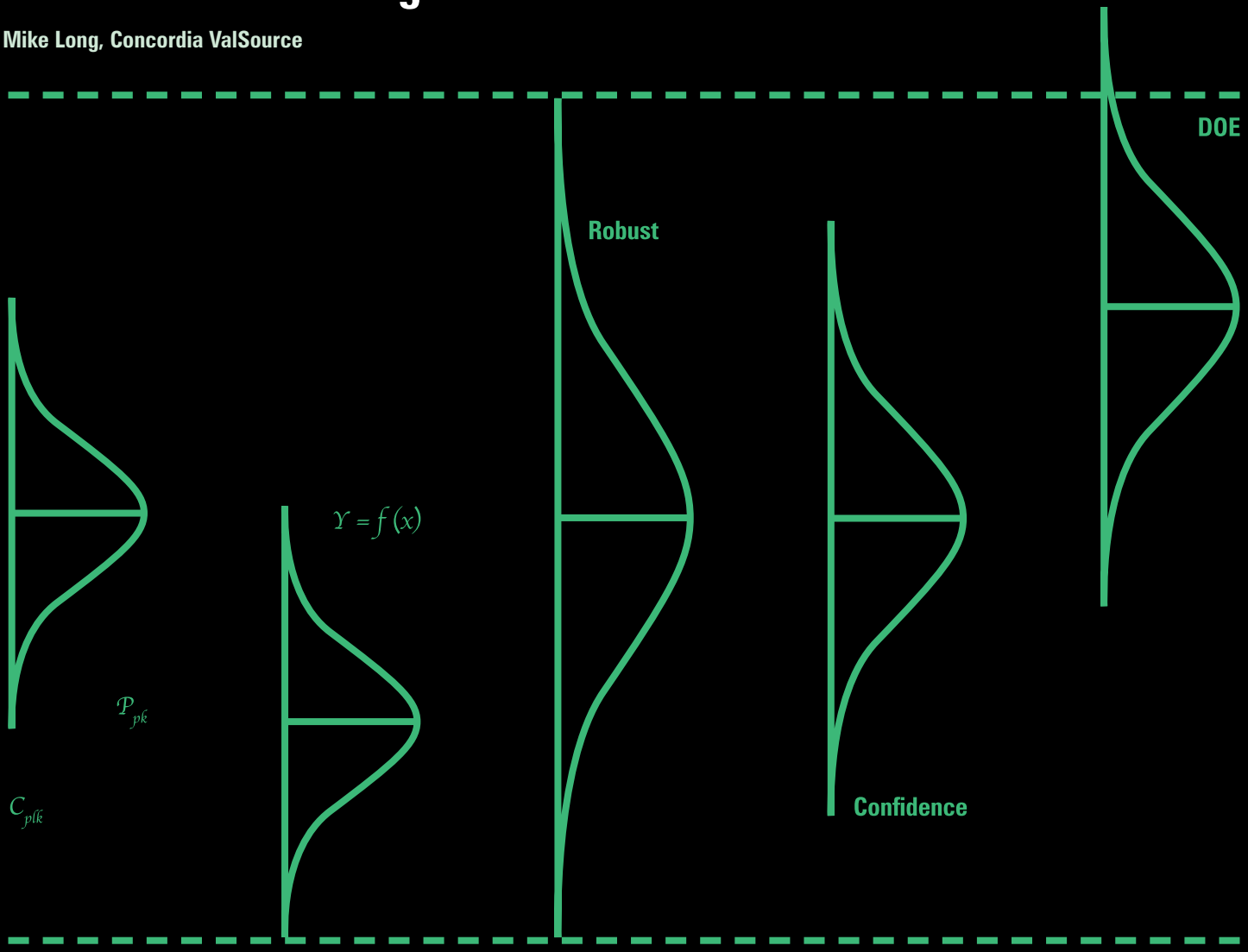
For more information on the BioAB and its related interest groups, please visit www.pda.org/Science-and-Regulatory-Affairs/BioAB.aspx.

About the Expert

E.J. Brandreth brings over twenty years of experience in the regulatory and QA fields. He has also led the process validation programs for five U.S. FDA CBER/EMEA product launches.

Risk and Statistics Serve as Tools for Solving Variation Riddles and Creating Robust Processes

Mike Long, Concordia ValSource



How much variation is acceptable in our products and processes? For such a simply stated question, the answer can be quite complex, especially when applied to drug product Stage 2 testing (Process Performance Qualification, or PPQ). It is a question industry needs to begin answering at the initiation of Stage 1 activities, with risk management as the key tool and driver in assisting to solve variation riddles and help drive knowledge management so industry can:

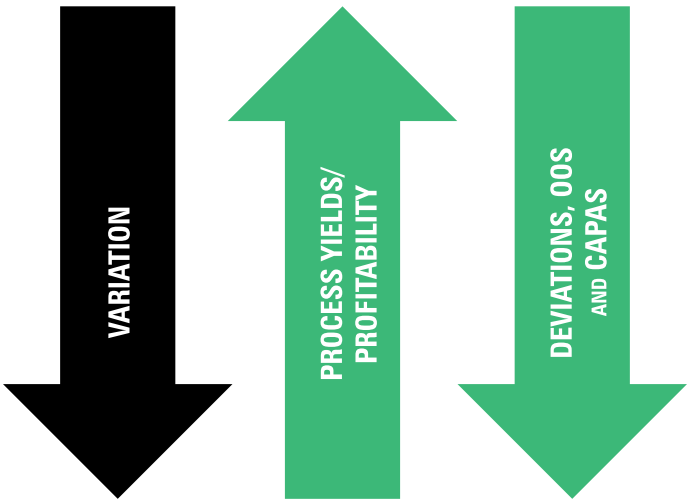
- Understand the *product*
- Understand the *process*
- Understand the *variables*
- Have *confidence* before going into commercial manufacture ***(1)***

As discussed in *Technical Report 60: Process Validation: A Lifecycle Approach,* control of variation is one aspect of the application of the enabling system of risk management. For it to be effective, risk tools need to be introduced early in Stage 1. This initial application will better help industry understand and control the amount of variation in its products and processes, the source of its origin and its ultimate impact on the patient. In essence, we are trying to create a means by which we can develop, and ultimately measure, the robustness of our products and processes. But first we must define the maximum amount of variation we are willing to accept in our product attributes for these robust products and processes to be developed. This requires a full embrace of the new lifecycle approach to process validation.

Article at a Glance

- "Line of Sight" approach can be used to assess variation
- CQAs with high severity ratings require higher testing standards
- Variations can be controlled using statistics and risk analysis

Figure 1 Effects of decreased variation on operations and quality metrics. Source: M. Long, PDA Annual Meeting, San Antonio, TX 2011 "Introduction to QbD for Suppliers: The first steps."



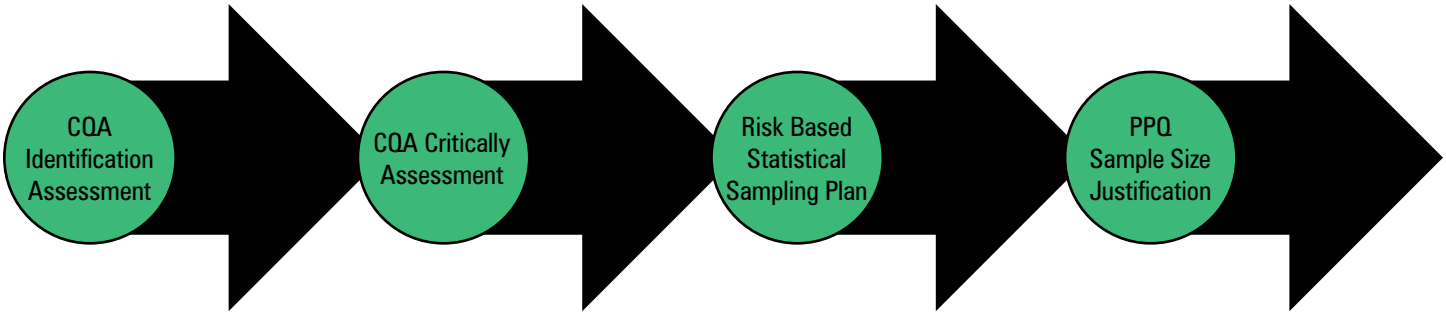
How do we get there? "Line of Sight" is how we can describe the manner in which variation can be assessed along the lifecycle. The amount of testing we perform during Stages 2 and 3 needs to have a clear path back to the attributes of the products we wish to deliver. It must also have a risk-based statistical justification ***(2).***

Why employ this approach? When we can measure, reduce and control variation, gains will be seen on both the operational and quality assurance sides of the business. Production and process yields will increase with reductions in variation. As yields increase, profitability advances will be seen. From a quality-system standpoint, reduction in variation will correlate to reductions in events like deviations, OOS, and CAPA (See **Figure 1).**

The following steps, embedded within Stages 1 and 2, provide the basis for this Line of Sight approach(see **Figure 2):**

- Initial definition of Critical Quality Attributes (CQAs)
- Criticality analysis of CQAs (also known as Continuum of Criticality)
- Criticality-based statistical approach for sample sizes
- PPQ sample size justification

Figure 2 Line of Sight: CQA Identification to PPQ Sample Size Justification



Sources: *Technical Report 60: Process Validation: A Lifecycle Approach*, 51-55, and Long, M. Baseman, H. and Henkels, W.D. "FDA's New Process Validation Guidance: Industry Reaction, Questions, and Challenges," *Pharmaceutical Technology,* Volume 35, Sept 2011.

The initial step in the process is to identify the product CQAs. There are different approaches used in industry when determining CQAs. An example of a risk tool that can be utilized is shown in **Table 1**. While there are different manners in which product quality attributes are identified as "critical," the answer eventually comes down to a "yes or no" for criticality. The attribute simply *is* or *is not* a CQA with "Potential CQAs" moving up to critical or down to noncritical as product and process knowledge increases.

Identify Risks with Assessments

After the initial CQA Assessment, the relative risk of the individual CQAs needs to be determined. Not all CQAs are

Table 1 Example of Quality Attribute Criticality Assessment

		Uncertainty		
		Low (Large amount of in-house knowledge, large body of knowledge in literature)	**Medium** (Some in-house knowledge and scientific literature)	**High** (No/little in-house knowledge, very limited information in scientific literature)
Severity	**High** (catastrophic patient impact)	**Critical**	**Critical**	**Critical**
	Medium (moderate patient impact)	**Potential**	**Potential**	**Potential**
	Low (marginal patient impact)	**Non-Critical**	**Non-Critical**	**Potential**

Source: *Technical Report 60: Process Validation: A Lifecycle Approach*, Page 53.

Table 2 Example CQA Continuum of Criticality Analysis with Relative Statistical Sampling Requirements

Critical Quality Attribute (CQA)	Severity of potential harms (effects)	Statistical Sampling Requirements
Potency / Bioactivity	High	+++
Plunger Glideability	Med	++
pH	Low	+

Sources: *Technical Report 60: Process Validation: A Lifecycle Approach*, 51-55, and Long, M. Baseman, H. and Henkels, W.D. "FDA's New Process Validation Guidance: Industry Reaction, Questions, and Challenges," *Pharmaceutical Technology*, Volume 35, Sept 2011.

Table 3 Example CQA Continuum of Criticality Analysis with Detailed Statistical Levels Assigned.

Critical Quality Attribute (CQA)	Severity of potential harms (effects)	Example Confidence and Proportion Requirements
Potency / Bioactivity	High	95/99
Plunger Glideability	Med	95/95
pH	Low	95/90

Sources: *Technical Report 60: Process Validation: A Lifecycle Approach,* 54, 84, and ISO 16269–6 *Statistical interpretation of data–Part 6: Determination of statistical tolerance intervals.*

Table 4 CQA Criticality Based PPQ Sampling for Drug Product, Combination Products, or Medical Devices

CQA Severity	*Discrete Data*	Discrete Data Sample Size *n:*	*Continuous Data* Note: Sample size determined by Test method chosen
	Minimum Population Proportion	*Zero Defects Allowed (95% Confidence)*	*Minimum Population Proportion (95% Confidence)*
High	.99	n = 299	.99
Marginal	.95	n = 59	.95
Low	.90	n = 29	.90

Sources: *Technical Report 60: Process Validation: A Lifecycle Approach,* 54, 84, and ISO 16269–6 *Statistical interpretation of data–Part 6: Determination of statistical tolerance intervals.*

equivalent from a risk standpoint. The impact of the failure of a CQA is on a continuum. Some will have a minor impact on patient safety, while others will have a major impact. The relative difference needs to be assessed with a method called the "Continuum of Criticality," which will eventually provide the basis for PPQ sample size justification ***(3).***

The Continuum of Criticality assessment is simple from a conceptual standpoint. CQAs that have a high severity rating should have a higher standard of testing applied to them as compared to those CQAs that have been determined to have a low severity. For discussion, we can look at three product attributes for a large molecule being filled into a syringe (potency/bioactivity, plunger glideability and pH). All have all been classified as CQAs. A simple risk assessment has been performed to determine the relative criticality for each (see **Table 2).** The analysis of this product example shows that we must test and assess potency/bioactivity to a higher level than pH. This is the point at which we are starting to determine the maximum amount of variation we will allow in our product and process, which creates a baseline minimum amount of robustness. It is now something we can target and begin to measure.

As the relative criticality has been assessed, there should be standard methods within organizations to tie these severity rankings to a statistical level. Using a typical confidence of 95%, we have applied 99%, 95% and 90% minimum population acceptance levels to high, medium and low severity bands respectively (see **Table 3).** What this means, practically, is the three CQAs in our example must meet at the least, with 95% confidence, the population levels shown. We now have assigned the minimum level of robustness we will allow for the CQAs.

Although we have assigned statistical levels that tie Line of Sight back to the relative risk levels of the CQAs, we have not determined their risk-based sample sizes. The number of samples will be determined by the manner in which the data the CQA is presented. If the data is continuous, we will have to take fewer samples than if ➤

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the data is discrete (pass/fail). An example of how to select sample sizes using ISO 16269–6 is provided in **Table 4** ***(4)*** **.**

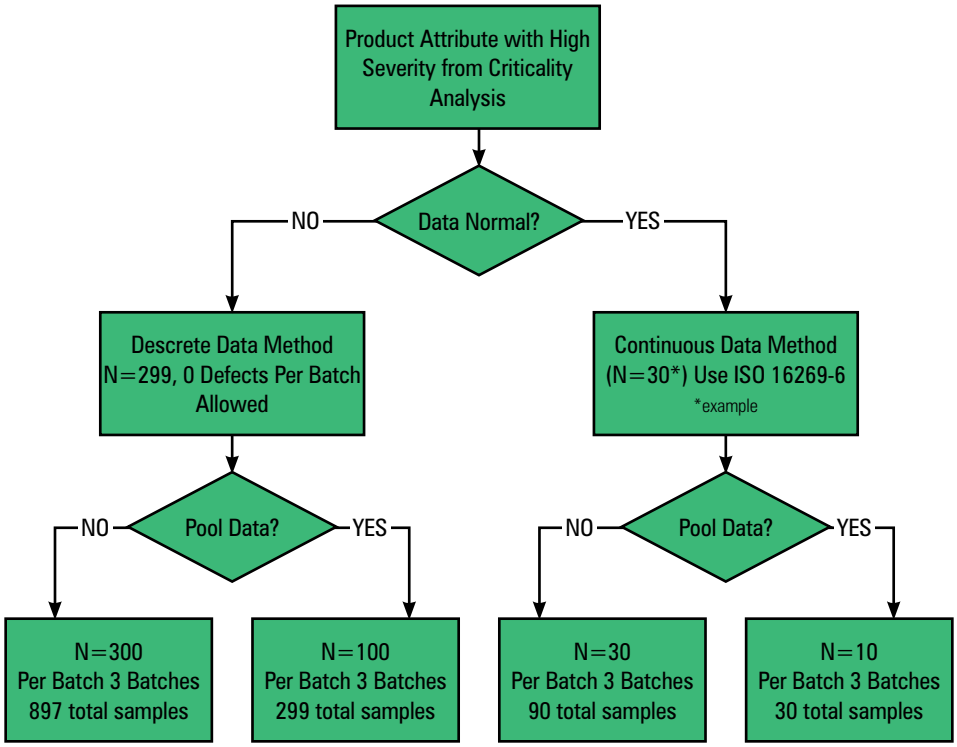
The amount of testing performed during development and clinical batches may assist in pooling of the samples. For example, if a given CQA output is shown to be substantially equivalent batch to batch, samples can be taken across each batch and pooled together, rather than performing the testing by just sampling within each batch. For a high severity CQA, **Figure 3** provides a decision tree that shows the difference in samples required if the data collected is discrete or continuous, pooled or not. As you can see, the range can be significant. But, the earlier in the lifecycle this analysis is performed and understood, the easier it is to plan.

Moving backwards in the lifecycle… the samples sizes we selected were based upon standard statistical methods using the type of data and variation seen in development, and tied to a relative severity level of the product quality attributes assessed to be critical to quality. This is our Line of Sight – this is how we begin to control variation and create robust products and processes.

Statistical Methods Control Variation

Robust processes require the identification and control of variation. This control begins the initiation of Stage 1 activities with the identification of preliminary CQAs, and executed with a Line of Sight approach tying sampling in PPQ directly back to CQAs through a methodical use of risk management and statistics.

Figure 3 Example of Decision Tree for PPQ Sample Size Justification



[Editor's Note: This article is based upon content being presented by the author at the *2013 PDA/ FDA Process Validation Workshop,* May 20-21 in Bethesda, Md. See p. 36 for more information.**]**

References

1. Long, M., Baseman, H. and Henkels. FDA's New Process Validation Guidance: Industry Reaction, Questions, and Challenges. *Pharmaceutical Technology;* 2011, 35: s16-s23 www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=738387.
2. Guidance for Industry Process Validation: General Principles and Practices, U.S. Food and Drug Administration: January 2011 www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070336.pdf.
3. *Technical Report No. 60: Process Validation: A Lifecycle Approach;* Parenteral Drug Association: 2013. www.pda.org/bookstore (accessed March 14, 2013).
4. ISO 16269-6 Statistical interpretation of data–Part 6: Determination of statistical tolerance intervals, ISO: 2005 www.iso.org/iso/catalogue_detail.htm?csnumber=38772.

About the Author

Mike Long has over 20 years of experience in the pharmaceutical and medical device industries. Currently, he is part of the management team at Concordia ValSource and a member of PDA's Science Advisory Board and the PDA Letter Editorial Committee.

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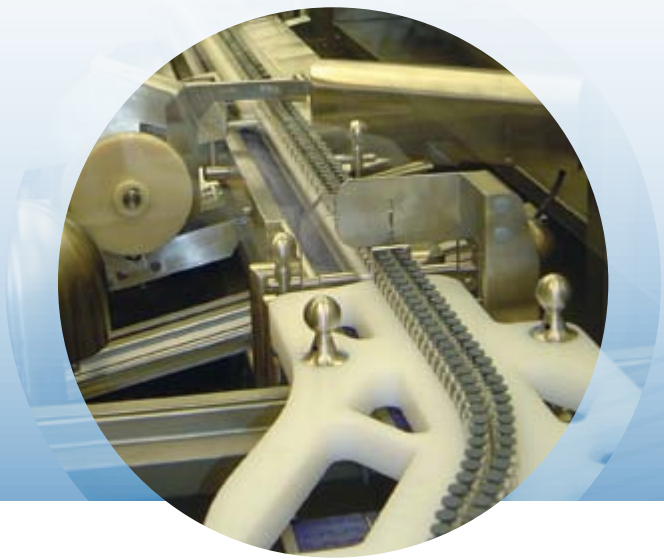

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4-6
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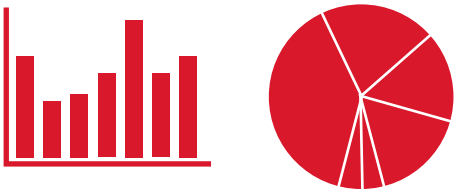
U.S. vs E.U. PROCESS VAL GUIDANCES

≠ indicates where the two guidelines suggest differences

= indicates where the two guidelines share similarities

2011 U.S. FDA Guidance		2012 EMA Draft
DEFINITION: "The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products."	≠	**DEFINITION:** "The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes."
PROCESS PERFORMANCE QUALIFICATION (PPQ) INTRODUCED WITH CONCURRENT RELEASE	≠	REFERS TO PROCESS VALIDATION IN A TRADITIONAL SENSE
Nonstandard drugs covered, e.g., orphan, radiopharmaceuticals, etc.	=	Nonstandard processes discussed
EMPHASIZES IMPORTANCE OF STATISTICS THROUGHOUT LIFECYCLE 	≠	STATISTICS ONLY EMPHASIZED IN CONTINUOUS PROCESS VERIFICATION 
CLEARLY ENDORSES CONTINUOUS PROCESS VERIFICATION	≠	CALLS CONTINUOUS PROCESS VERIFICATION "AN ALTERNATIVE APPROACH"
Purports to align with ICHQ8, Q9, Q10, and Q11	=	Purports to align with ICHQ8, Q9, Q10, and Q11

Special thanks to Hal Baseman, Mike Long, and Scott Bozzone, PhD, for their assistance with this infographic.

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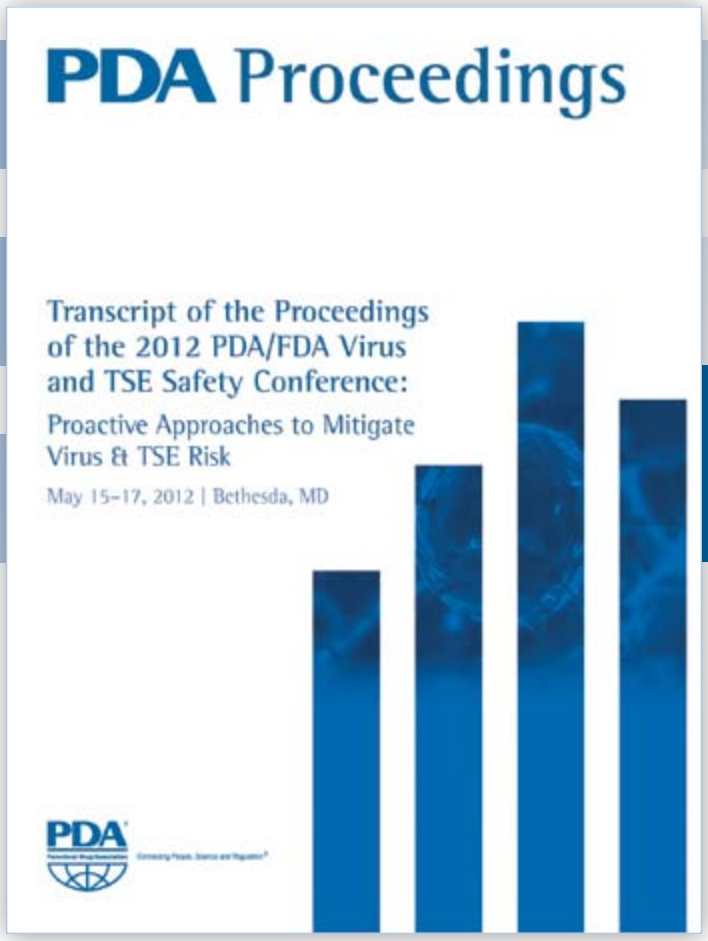

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U.S. FDA Offering "Q" Metrics for Payers – A Good Idea

An interview with Amgen's Martin VanTrieste

Walter Morris, PDA

In March, the PDA Letter *sat with Amgen's* ***Martin VanTrieste*** *to discuss the impact quality-related problems in the pharmaceutical industry are having on the marketplace for drug products. Prompting the conversation was the article by two U.S. FDA officials in which they suggested that the lack of market reward for high-quality products. The FDA authors proposed that the Agency could help consumers and healthcare payors better understand the importance of quality by offering "meaningful manufacturing quality metrics." The* PDA Letter *analyzed this article and other regulatory initiatives worldwide (see the cover story of the March 2013* PDA Letter*).*

The entire interview with Martin was recorded and is available at www.pda.org/pdaletter. Below are selected questions and answers from the interview.

PDA Letter: Thanks for giving more of your valuable time to PDA and the *PDA Letter,* Martin. we always appreciate the opportunity to work with you. We last interviewed you on your work with PDA on the U.S. FDA aseptic processing guidance. Now, we are talking about a completely different subject.

Let me ask you the toughest question right up front, is public confidence in the quality and safety of the drug supply eroding in the wake of all the high-profile quality breakdowns seen, basically starting with the Heparin situation several years ago?

VanTrieste: As we all know, the media and the American public have a short memory and most people probably haven't even head or remember much about the Heparin events. And, fortunately, there has not been a significant event leading to deaths since the heparin events. Therefore, I would conclude that the public has not lost confidence in any measurable manner in the medicines. However, when another event occurs, and if they occur in a more consistent manner, the American public will lose confidence in their medicines. This could lead to all kinds of unintended consequences such as patients stopping their treatments out of fear leading to a worsening of their condition.

PDA Letter: In an article by the FDA's **Janet Woodcock,** MD, and **Marta Wosinska,** PhD, they assert that quality is too expensive, particularly for generic manufacturers of injectable products, in the face of tight price competition and a marketplace that does not reward high quality. I know you work for an innovator firm, but what do you think of this revelation? Is it true, in your opinion?

VanTrieste: I don't read the article that way. I believe that Dr. Woodcock is saying that payors, providers and patients cannot ascertain the quality level of their medicines and therefore quality cannot be rewarded in the marketplace. Therefore, the FDA is looking for ways to provide these stakeholders with a transparent and user friendly way of determining the quality of the medicines they are consuming, delivering and reimbursing. One method suggested was that the FDA would issue a quality grade similar to what health departments do for restaurants, which allows the consumer to decide if they want to eat at a deli that receives a "C" versus one that receives an "A." The theory being is that the consumer will choose the higher quality product, forcing the competition to improve their quality level to stay competitive in the marketplace, thus rewarding quality and leveling the playing field between all manufacturers.

PDA Letter: Let's not speculate as to whether or not FDA can successfully change the minds of buyers and payors to consider quality, and maybe even pay more for quality. The question for you, as someone who is a student of quality management across many consumer industries, do you feel Quality's time has come? In other words, do you think consumers should start paying as much attention to drug product quality as they do to the quality of their cars, iPhones and potato chips?

VanTrieste: I absolutely do believe that in most cases consumers will pay for quality and, more importantly, will reject poor quality products. But the real change will be around the actions of payors and providers. In our society where individuals sue very quickly, I would image that payors and providers would be very hesitant to prescribe or require the use of a medicine that received a grade of a "C" when one with an "A" is available. In the case where a grade "C" medicine is required instead of the grade "A", the prescriber and/or payor would be open to significant legal risk when significant adverse events or product complaints occur. The fear of lawsuits will drive the providers and payors to use the best grade medicine available, thus raising quality at all manufacturers who want to be successful in the marketplace.

PDA Letter: Would this be advantageous to companies like Amgen that invest heavily in their quality systems? Could you see ads in the future saying, "You won't find a better quality drug than ours"? Would this kind of marketing be good or bad for the industry, in your opinion? ➤

I don't believe that patient safety should ever be used as a competititive advantage

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VanTrieste: I don't believe that patient safety should ever be used as a competitive advantage. This reminds me of the old TV commercials for Volvo when I was a kid that stated Volvo invented the seat belt which has saved thousands if not millions of lives. The commercial went on to say that consumer safety was too important, and that even though Volvo had the patent for the seat belt, that they would not enforce that patent, and allow all car makers to incorporate seat belts into their designs. I am very grateful for this fact, since my two oldest daughters were in a horrific automobile accident a few years ago, and I am convinced that they would be dead or seriously injured if they were not wearing their seat belts. At Amgen, our strong culture of continuous improvement helps us meet our most important commitment – to provide patients with high quality, reliably supplied medicines. This commitment is why Amgen not only allows me, but encourages me to share information about our quality system.

PDA Letter: Does the public really need FDA's prodding to open their eyes to the need for high quality drugs, or would more high-profile incidents where patients get hurt or die and drug shortages resulting from poor quality do the job?

VanTrieste: We all need the FDA to serve this role. When I take my Statin every morning, I look at a little white pill; I have no way of determining the quality of that little white pill. I can't determine if the medicine will work, if it will hurt me or what other unintended consequence may occur. I have to have confidence and trust that the system will protect me. However, as a member of this industry, I do know that not all companies have the same quality culture. I also know that not all products are made to the same quality standards and I feel I have sufficient industry knowledge to make informed decisions about the medicines my family and I consume. I believe that all customers should have the same ability as I do to make an informed decision about the quality of their medicines.

About the Expert

Martin VanTrieste is the senior vice president of Quality at Amgen. He is responsible for all aspects of quality assurance, quality control, compliance, environment, health and safety along with training at Amgen.

snapshot

PDA to Comment on WHO GMP Draft Guidelines

Denyse Baker, PDA

The Regulatory and Quality Advisory Board (RAQAB) has a very active agenda for regulatory comments this spring, especially for new proposals coming from outside the United States. Notably, these proposals involve the World Health Organization (WHO) and European health authorities.

WHO has proposed a change to their publication, *Good Manufacturing Practices for Pharmaceutical Products: Main Principles.* In response, PDA encourages WHO to adopt existing approaches, such as PIC/S GMP guidelines, rather than publishing another set of regulatory standards. In addition, WHO has announced two more GMP-related documents available for comment: *General Guidance for Inspectors On "Hold-Time" Studies* which identifies aspects that should be considered in the design of the hold-time study and *Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product* which is designed to assist applicants on the preparation of the quality module of product dossiers for multisource products by providing format, technical and other general data requirements.

There have been several new proposals coming from European health authorities as well

There have been several new proposals coming from European health authorities as well, which modify aspects of current GMPs. RAQAB currently has task forces developing responses to the following European Commission draft documents: *Guidelines On The Formalised Risk Assessment For Ascertaining The Appropriate Good Manufacturing Practice For Excipients Of Medicinal Products For Human Use* and *Guidelines On The Principles Of Good Distribution Practices For Active Substances For Medicinal Products For Human Use*, plus comments on proposed changes to the Commission's template used by qualified persons for their declaration concerning GMP compliance of investigational medicinal products manufactured in non-EU countries.

PDA will update its members regarding the status of these comments.

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

Office of Generic Drugs Director Resigns

Effective March 15, **Greg Geba,** MD, has resigned from his U.S. FDA position as Director of the Office of Generic Drugs (OGD), citing the challenges of some of OGD's functions in the new Office of Pharmaceutical Quality (OPQ). In the interim **Kathleen Uhl,** MD, will head OGD as acting director while the Agency looks for a replacement for Geba.

In 2012, **Janet Woodcock,** MD, CDER, proposed elevating OGD to a "super-office." Previously, it fell under the Office of Pharmaceutical Science (OPS).

CDER Hires New Deputy Director

Richard Moscicki, MD, has been appointed Deputy Center Director for Science Operations within the CDER branch of the U.S. FDA. In his new role, Moscicki will help CDER to regulate over-the-counter and prescription drugs within the United States by overseeing the development of CDER programs. Previously, he served as VP, Clinical Development at the Genzyme division of Sanofi.

New Guidance Concerns Device Recalls

In February, the U.S. FDA announced availability of the draft guidance, *Distinguishing Medical Device Recalls From Product Enhancements; Reporting Requirements*. This guidance is supposed to offer clarifications for industry for identifying when potential changes to a device become recalls. The guidance provides information on how to distinguish these changes from product enhancements as well as identifies reporting requirements for both recalls and enhancements.

Comments on the draft guidance are due May 23.

Interactive Review Process Guidance for Device Submissions Now Available

The U.S. FDA released in early March a draft guidance that updates the Agency's interactive review process for premarket medical device submissions to reflect changes under MDUFA II and III. The document also includes guidelines on additional types of communication to increase efficiency during the review process.

Comments are due June 3.

Key Regulatory Dates

Comments Due

May 23 — New Guidance Available Concerning Device Recalls

June 3 — Interactive Review Process Guidance for Device Submissions Now Available

Europe

EU Releases Final GDP Guidelines

On March 7, the European Union released final GDP guidelines for wholesale distributors of medicinal products within the European Union. Wholesale distributors must now maintain quality systems outlining responsibilities, processes and risk management objectives in relation to distribution of pharmaceuticals as part of overall quality management. These quality systems must encompass the company's entire organizational structure, procedures, processes and resources to ensure that products delivered are of the highest quality and integrity.

The guideline also addresses requirements for personnel, monitoring, facilities, hygiene, equipment and training among other areas.

Asia-Pacific

China Plans Centralized Food and Drug Agency

The Chinese legislature plans to approve a new ministerial-level Agency, the General Administration of Food and Drug. This Agency would be responsible for regulation of food and drug products, and would be modeled on the U.S. FDA. Currently, this responsibility mostly falls under the country's State Food and Drug Administration (SFDA), which is affiliated with the Ministry of Health, as well as 13 other government agencies.

The government hopes that by developing a centralized agency it will avoid repeats of recent incidents involving contaminated food and drug products.

South America

Argentina's Reg Body Enacts New Laws

ANMAT, the Argentinian regulatory authority responsible for medical devices, has authorized changes to the country's General Law for Medical Devices involved portions of the law concerning device registrations.

Under these changes, foreign manufacturers now must provide a commercialization history in all the countries where device products are sold, send a letter from the manufacturer to a foreign manufacturer's Argentinian market importer that assures to inform the importer of any recall and other safety actions involving a device and submit a Certificate of Free Sale or Country of Origin Approval from any country to ANMAT.

Will FDA Combo Rule Help Pharma with Quality Systems?

Anna Lundén, Key2Compliance AB and Philippe Joly, EasyGMP

Beginning on July 22, any company that develops, manufactures and distributes a "combination" product to the U.S. market needs to comply with 21 CFR 4. This new U.S. FDA rule codifies CGMP requirements applicable to combination products. Many companies are probably now in the process of doing gap analyses and evaluating the steps needed to be in compliance with this new rule. According to the FDA, this should not be an issue for those companies as the estimated time for implementation is 25 hours.

FDA says the requirements are not new and that this new rule merely clarifies the possibility to use a **streamlined approach** instead of implementing two quality systems in parallel.

The information below will explain parts of the new rule and will present a possible approach to implement a quality system.

But first, let us define a combination product. As defined in 21 CFR 3, it is a combination of two or more regulated components that are physically, chemically or otherwise combined or mixed and produced as a single entity, such as:

- A drug and a device
- A drug and a biological product
- A device and a biological product
- A drug, a device and a biological product

Combination products can be further categorized as either a single-entity combination product or a co-packed combination product (for specific examples of both, see **Figure 1).**

21 CFR 4 states that CGMP and quality system requirements for each type of product already exist (see **Table 1** for a listing of these quality system requirements).

Table 1

Drug products	21 CFR2 10/211, Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs/Finished Pharmaceuticals
Medical Devices	21 CFR 820, Quality System Regulation (CGMP) for Finished Devices
Biological Products	21 CFR 600 through 680, CGMPs for Biological Products
HCT/Ps (Human Cells, Tissues, and Cellular and Tissue-based Products)	21 CFR 1271, Current Good Tissue Practices

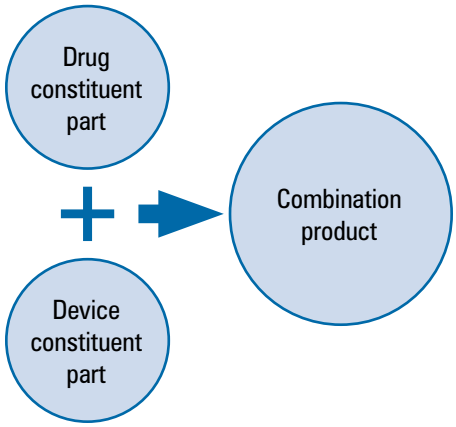
Biological products, however, present a challenge, as a biologic is by definition a drug or a device and a HCT/P (Human Cells, Tissues, and Cellular and Tissue-based Product) that must adhere to "good tissue practice" requirements.

Ultimately, a combination product is a drug, device and/or biological product with the CGMP/quality system requirements for combination products built either on drug CGMPs or on device quality system regulations.

With this new rule, FDA wants to provide a "clear and transparent roadmap" about how to apply these different regulations, and offer flexibility depending on product complexity.

The suggested model that emerges from the rule is that each company has the freedom (and responsibility) to identify a basis for a quality system that is either based on drug CGMPs or device CGMPs/quality systems on the manufacturing process. Based on where in the process the different products (see **Figure 2)** are actually combined, the company has various options. When manufacturing of the drug, device or biologic is done separately, the firm can choose to have a quality system based solely on the regulation pertaining to each product**.** (There is also an overall requirement for the organisation to comply with all applicable requirements for the combination product as a whole.) But at some point the different products will be combined. From that step, both drug and device quality system rulers will apply.

Figure 2



As mentioned before, manufacturers can choose the streamlined approach. This means that if the firm's quality system is based on 21 CFR 210/211, 21 CFR 4 clarifies additional device requirements that must be implemented for a firm that has a 21 CFR 820-based quality system (see **Table 2).**

And when analyzing this from a broader perspective, an interesting picture

Figure 1

Single Entity	Co-Packed
• Device coated or impregnated with a drug or biologic • Drug-eluting stent; pacing lead with steroid-coated tip; catheter with antimicrobial coating; condom with spermicide • Prefilled syringes; insulin injector pens; metered dose inhalers; transdermal patches	• Drug or biological product packaged with a delivery device • Surgical tray with surgical instruments, drapes, and lidocaine or alcohol swabs

Table 2

Quality systems based on 21 CFR 210/211 add these requirements from Device CGMP	Quality systems based on 21 CFR 820 add these requirements from Drug CGMP
820.20 Management responsibilities	211.84 Testing, Release, reject of Component, Containers and Closures
820.30 Design controls	211.103 Calculation of yield
820.50 Purchasing controls	211.132 Tamper-evident packaging for OTC
820.100 Corrective and Preventive Action	211.137 Expiration dating
820.170 Installation	211.165 Testing and release for distribution
820.200 Servicing	211.166 Stability testing
	211.167 Special testing
	211.170 Reserve samples

unveils. Thoughts from the FDA about quality systems were published in its September 2006 guidance on CGMPs. That guide in itself is for information mainly, and does not introduce any new rules. It merely provides an in-depth comparison of CGMPs for drugs with other quality systems including 21 CFR 820 and ISO-based systems such as ISO9001 and ISO13485. If we also consider ICH guidances related to quality systems (Q8/Q9/Q10), and comprehensive efforts between FDA and other device stakeholders to harmonize the device CGMPs in 21 CFR 820 with ISO 13485 ***(1),*** there is a path for implementing effective quality systems.

For a company that deals with combination products (and for others as well) and is ready to implement requirements under 21 CFR 820 and ISO 13485 (focusing on design controls, management controls and CAPA), there is an opportunity to implement a comprehensive and efficient quality system that can be understood by everybody, endorsed by management and bring value to the organization.

With this new rule, FDA wants to provide a "clear and transparent roadmap" about how to apply these different regulations

References

1. www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/default.htm.

About the Authors

Anna Lundén is part owner in Key2Compliance AB, a training and consultancy firm specializing in GMP compliance and quality systems training in Europe. Her background involves more than 15 years working with training, auditing and consulting for European pharmaceutical and medical device companies handling both EU and FDA requirements.

Philippe Joly has several years of experience in GMP training, consulting and auditing in the United States and Europe for both the pharma and device industries. He is a senior consultant with EasyGMP LLC.

Learn About New Regulations at Process Val Workshop

2013 PDA/FDA Process Validation Workshop • Bethesda, Md. • May 20-21 • www.pda.org/processval2013

Scott Bozzone, Pfizer

Do you want to find out and learn the latest on process validation? How about listening to and interacting with the leading regulators, industry experts and consultants on the subject? If so, the planning committee urges you to attend the upcoming *2013 PDA/FDA Process Validation Workshop.* Here, U.S. FDA and European regulatory representatives will present the latest process validation regulations, including FDA's January 2011 guidance, ICH Q8-11, EMA's March 2012 draft guideline and EMA's upcoming planned revision of Annex 15 on validation and qualification. The new *PDA Technical Report 60: Process Validation: A Lifecycle Approach*, which was published in February 2013, will be available and discussed as well.

Industry experts will share their experiences with the benefits and challenges of process validation, including validation practices for both new and legacy products.

Attendees will learn to distinguish between continued and continuous process verification

The workshop consists of:

- Six sessions devoted to specific areas, such as the process validation lifecycle from where to begin (Process Design - Stage 1) through Commercial Production (Stage 3)
- Case studies of small and large molecules
- The Quality Risk Management Interest Group's session, which will focus on describing the QRM enabling tool and practical examples of its effective use

Some recent concepts have been shown to be confusing or conflicting, so if you're involved in this area we urge you to plan to attend to learn the latest in process validation. Attendees will learn to distinguish between continued and continuous process verification, as well as when and how to apply statistical approaches and PAT applications. In addition, attendees will also learn how to establish a continued process monitoring plan.

So, come attend the *2013 PDA/FDA Process Validation Workshop* and learn how process validation can help you and your organization today!

Joint Reg Conference Offers Key Learning Objectives

2013 PDA/FDA Joint Regulatory Conference • Washington, D.C. • Sept. 16–18 • www.pda.org/pdafda2013

David J. Cummings, CDER, U.S. FDA and Mahesh Ramanadham, CDER, U.S. FDA

Each year PDA and the U.S. FDA join forces with the common goal of sharing information with the pharmaceutical industry. The *2013 PDA/FDA Joint Regulatory Conference* serves as the forum for this exchange. In general, participants can take away best practices that can be readily applied upon returning to their organization and interact directly with global regulatory agency representatives to pass along those insights to colleagues

At this year's conference, participants will be able to share information and explore a variety of current topics that challenge today's managers, including: empowering and supporting leadership, maintaining a robust quality management system, ensuring high quality product throughout the lifecycle, monitoring process performance and product quality, maximizing the effectiveness of supplier management programs and strengthening the quality culture.

Today's industry is faced with a number of global and organizational challenges

Today's industry is faced with a number of global and organizational challenges with different priorities and objectives. It is important that leadership within the medical products industry be prepared to fulfill the objectives for quality assurance, access and risk management for all patients and healthcare providers.

PDA's Training and Research Institute (TRI) will be offering six courses designed to expand on what you've learned immediately following the conference on Thursday and Friday. We invite you to take advantage of the opportunity to extend your stay for a day or two and make the week an even more valuable experience.

Workshop Showcases Investigations Methods

2013 PDA/FDA Improving Investigations Workshop • Washington, D.C. • September 18–19 • www.pda.org/investigations2013

Co-chairs Anders Vinther, PhD, Genentech, and Rick Friedman, U.S. FDA

Building on the success of the *ICH Q10 Pharmaceutical Quality System Workshop for Executive Management* held in fall 2012, PDA and the U.S. FDA continue to hold workshops that will help industry implement robust quality systems that ensure a sustainable state of control. The *Improving Investigations Workshop* is designed to share current regulatory expectations and deliver practical solutions to improve a crucial part of a CGMP-compliant quality system: the capability to do investigations of failures, complaints and deviations.

The workshop, which immediately follows the *2013 PDA/FDA Joint Regulatory Conference,* will include FDA and industry experts speaking about investigating the root causes of manufacturing and quality problems, the adverse impact of a poor investigation and tools that are being used successfully in the industry to determine root causes to better fulfill drug quality and business goals. They will share their insights on how to assess and conduct thorough investigations that lead to sustainable improvement to quality and compliance.

Ultimately, assuring a robust investigation program is crucial to all pharmaceutical companies, since "lack of adequate investigations" continues to be a top inspection observation globally.

Interactive breakout sessions will offer ample opportunities to share and learn experiences and ideas that will allow attendees to apply session knowledge and best practices to case studies in areas such as:

- Lab investigations (investigating out-of-specification results)
- Multi-site operations investigations
- Supplier investigations
- Expectations and benefits of a well-executed investigation
- Scoping and executing an investigation
- Evaluating effectiveness of corrective and preventive actions
- When to close an investigation

PDA Parenteral Drug Association

4-6 June 2013
RAMADA Hotel
Berlin-Alexanderplatz
Berlin | Germany

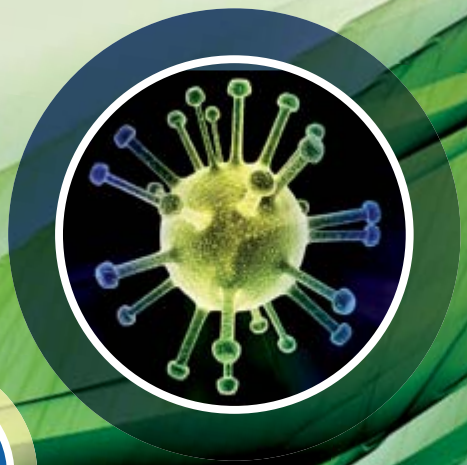
The Parenteral Drug Association presents...

2013 PDA European

4th Virus & TSE Safety Forum

- Development of new technologies for virus detection
- Knowledge of mechanism of action, in effectiveness and robustness of virus removal/inactivation by specific unit operations
- Application of QbD principles, including risk mitigation strategies
- Discussion about new and emerging viral treats such as hepatitis E and circovirus
- Virus contamination of cells or vaccines and risk mitigation strategies will be considered as well

The TSE Safety Forum will start with a scientific overview about BSE and vCJD. The current situation related to testing of human plasma or blood on vCJD and the availability of reference materials will be reported.



Register by 5 April 2013 and SAVE!

WORKSHOP | CONFERENCE | EXHIBITION

https://europe.pda.org/VirusTSE2013

Stay Ahead of the Curve at the 2013 Micro Conference

PDA 8th Annual Global Conference on Pharmaceutical Microbiology • Bethesda, Md. • October 21–23 • www.pda.org/microbiology2013

Osama (Sam) Elrashidy, Bayer Healthcare Pharmaceuticals, and Marla Stevens-Riley, PhD, U.S. FDA

Are you staying ahead of the curve? That is, are you or your organization in a position to anticipate or initiate the latest developments in the field of pharmaceutical microbiology? Do you or your organization practice proactive behavior with regard to pharmaceutical manufacturing by acting in advance of a future crisis rather than simply reacting to it, or worse, burying your head in the sand? With the increased globalization of pharmaceutical manufacturing and regulatory demands, emerging technologies and the continued identification of new sources and types of contamination, it can be difficult to judge whether or not you are ahead or behind.

The planning committee for the *PDA 8th Annual Global Conference on Pharmaceutical Microbiology* is working hard to deliver a program for the 2013 conference that can assist you with staying ahead of the curve and practicing proactive microbiology. This annual conference is dedicated to advancing science and regulation for global pharmaceutical microbiology by introducing the best practices of today and innovations of tomorrow.

This three day conference will provide a forum for discussion and debate for the pharmaceutical microbiology community of industry professionals and regulators by offering peer-reviewed presentations and poster sessions, panel discussions, vendor exhibits, training courses, and opportunities to network with leading scientists and engineers.

So, begin moving ahead of the curve today by practicing proactive behavior and plan to attend the *PDA 8th Annual Global Conference on Pharmaceutical Microbiology* this October.

Secure Your Place for the Supply Chain Workshop

2013 PDA/FDA Pharmaceutical Supply Chain Workshop • Bethesda, Md. • June 3–5 • www.pda.org/supplychain2013

Sue Schniepp, Allergy Laboratories

The *2013 PDA/FDA Pharmaceutical Supply Chain Workshop* planning committee is hard at work planning the next supply chain integrity meeting. Titled *Pharmaceutical Supply Chain Integrity: The New Horizon,* this unique event is designed to solicit participants' ideas on a wide variety of current and future supply chain issues facing the pharmaceutical industry.

The workshop will open with a benchmarking session where audience members will hear how other industries and organizations have successfully dealt with supply chain integrity issues. Scheduled to speak are representatives from the automobile and food industries as well as the U.S. Department of Homeland Security; the event planners have allowed ample opportunity to ask questions of these speakers. Following the opening keynote address, participants have the opportunity to choose between two discussion topics: "Securing the Future Supply Chain" and "Supplier Key Performance Indicators."

The first day concludes with a combined session on managing contractual arrangements and sets the stage for the second day of the workshop. The second day begins with two different discussion topics for participants to converse on. The focus of these topics will be "Supply Chain Communications" and "Effective Auditing."

In addition to the breakout discussions, participants will also hear about raw material quality standards, pharmaceutical supply chain import compliance and California's emerging standard for tracking and tracing prescription drug packages.

So, mark your calendars now and plan on attending this one-of-a kind workshop intended to offer practical solutions and best practices for managing supply chain integrity now and in the future.

Protect Drugs, Biologics With Container Closure Systems

2013 PDA/FDA Container Closure Components and Systems Workshop • Bethesda, Md. • May 14-15 • www.pda.org/containerclosure2013

Diane M. Paskiet, West Pharmaceutical Services and Mary G. Foster, Aphena Pharma Solutions

The model for today's pharmaceutical quality management system (QMS) is linked to different stages of the drug product lifecycle. Quality attributes are multi-dimensional, spanning a range of considerations from selection of container closure components to system compatibility, functionality, performance and stability, including protection of product as well as delivery to the patient. By attending the *2013 PDA/FDA Container Closure Components and System Workshop*, you will learn about the materials used in container closure systems and current advances to improve properties for parenteral drug products

Packaging materials have a lifecycle that must be understood relative to use with the finished dosage form. Potential defects can be defined in a systematic manner and help lead to decisions for the application of the first packaging process, which includes: multivariate data analysis, incoming assessments, in-process and finished goods, AQL's and related stability testing. Quality by Design (QbD) principles will be highlighted, and the risk analysis processes described supporting final decisions on which packaging materials will be selected to protect the dosage form over its assigned expiration date.

The packaging and distribution process is a critical dimension to provide details on the lifecycle of not only the drug/biologic ingredients, but also the lifecycle of the packaging materials, including those used to distribute the finished dosage form to the final end user. A recent survey revealed that 81% of biopharma companies are outsourcing their distribution logistics. There is a very clear shift in how we should view cold chain logistics, especially with the growth of biologically-derived drugs and vaccines.

Regulators as well as industry experts will be featured at the one-and-a half day workshop, bringing insight into comprehensive planning for suitable container closure systems for today's demands that go beyond past concerns.

Experts to Discuss Assuring Glass Quality at Conference

2013 PDA/FDA Glass Packaging Conference • Bethesda, Md. • May 15-16 • www.pda.org/glass2013

Ronald G. Iacocca, PhD, Eli Lilly and Company and Cesar Matto, CDER, U.S. FDA

On behalf of the programming committee and PDA, we would like to invite you to attend the third annual *PDA/FDA Glass Packaging Conference*. This year's program represents ongoing efforts to continue the dialog on glass quality and materials considerations for primary parenteral glass packaging. The session topics were selected to address key issues that the pharmaceutical industry faces. The program ranges from the selection of raw materials used to manufacture glass components to the regulatory documents required to qualify glass.

Logically, the conference begins with a discussion on the raw materials that are used to make pharmaceutical glass. Slight changes in glass quality have been shown to have noticeable impact on drug product quality; therefore control, or at least an understanding, of the materials going into the glass is now a requirement for pharmaceutical manufacturers. The flow of the presentations then moves to vial formation, where topics on the formation of both tubing and molded vials will be discussed.

This year's program represents ongoing efforts

Presentations by **Carol Rea Flynn, Desmond Hunt,** PhD, **John Shabushnig,** PhD, and others will provide valuable information on the status of glass delamination, new U.S. Pharmacopeia chapters that address matters of evaluating glass quality and the impact of glass particles on product quality.

The final session moves to a broader discussion of glass in the pharmaceutical industry, where talks will be given on how to minimize glass damage on manufacturing lines and during transportation.

We hope you agree that the information to be presented offers critical insight and information on current issues for glass used in parenteral packaging. The committee looks forward to your presence at the conference.

Virus and TSE Safety Forum Focuses on Emerging Issues

PDA Virus & TSE Safety Forum 2013 • Berlin, Germany • June 4-6 • https://europe.pda.org/virustse2013

Co-Chairs Kurt Brorson, PhD, CDER, U.S. FDA and Hannelore Willkommen, PhD, Regulatory Affairs & Biological Safety Consulting

Biopharmaceutical and plasma-derived medicines involve a complex, multi-step manufacturing process which entails significant risks, particularly from viral contamination. Sources of this sort of contamination include source materials, cell culture components, human involvement, and cell banks. Minimizing risk in this area involves a comprehensive and rigorous approach to process design, operational control, and maintenance. A robust program should be in place to identify potential sources of viral contamination hazards and to mitigate those risks by testing and clearance strategies. Moreover, risk management should incorporate new information; subtle changes or anomalies throughout the lifecycle may introduce new significant hazards that should be identified, evaluated and appropriately addressed. This is a rapidly evolving field, founded in principles outlined in ICH Q5A, where significant advances are made each year.

For these reasons, we invite you to attend the upcoming PDA European *Virus & TSE Safety Forum*. This forum will provide a forum for regulators, subject matter experts, leading biopharmaceutical companies and firms with enabling technologies (e.g., filters, chromatography, testing services, etc.) to discuss new viral clearance and testing technologies, new emerging safety viral safety issues (e.g., HEV and PARV 4), strategies for TSE risk mitigation, regulatory trends such as implementation of Quality by Design, and lifecycle approaches to quality risk management.

This is a rapidly evolving field, founded in principles outlined in ICH Q5A

A pre-symposium workshop held in the same venue the day before will discuss new advances in virus filtration and quality control and standardization of virus spike preparations. This area has advanced significantly since the release in 2008 of *PDA Technical Report No. 41: Virus Filtration* and in 2010 of *PDA Technical Report No. 47: Preparation of Virus Spikes Used for Viral Clearance Studies.* These two foundational documents have served as valuable educational tools for individuals charged with process development and validation activities. The workshop will build on this understanding and discuss important advances since release of these two technical reports.

Aseptic Processing – Sterilization Conference Returns to Chicago

2013 PDA Aseptic Processing-Sterilization Conference • Chicago, Ill. • June 20-21 • www.pda.org/aseptic2013

Ken Paddock, Baxter Healthcare

As innovation and best practices continue to be critical elements in the manufacture of sterile products, the annual *PDA Aseptic Processing-Sterilization Conference* is proud to present some of the most highly qualified experts to share their experiences in the development, validation and ongoing control of aseptic processing and terminal sterilization programs. The conference provides participants with a comprehensive review of state of the art practice including media fills/process simulation, risk assessment/mitigation, parametric release, biofilm eradication, container/closure integrity, advanced aseptic processing and novel sterilization technologies. Regulatory, pharmacopeial and industry leaders will provide insight on impending and evolving requirements for regulatory standards, pharmacopeial standards and industry guidance documents such as PDA technical reports. An "Ask the Experts" session will also be featured at the close of the conference.

In addition, PDA will host an exhibition of leading manufacturers and suppliers who will showcase new technologies and trends.

Technical Reports Mined to Create Distinct TRI Courses

By Bethanne Bond and Stephanie Ko, PDA

PDA's Training and Research Institute (TRI) has substantially increased its offering of new and unique courses to the pharmaceutical industry that are offered *nowhere else*. That's because these courses are based on PDA's very own technical reports and PCMO (Paradigm Change in Manufacturing Operations℠) documents, reflecting the best practices currently available in the industry.

So, how are these courses developed? First, we look at relevant technical reports. Each technical report is developed by a specialized task force comprised of volunteers who collaborate with other subject matter experts from industry, academia and/or government agencies on a specific topic. There is a significant peer review process prior to publishing a technical report, including reviews and approvals by PDA's Advisory Boards and the PDA Board of Directors.

The instructor and course developer play an important role in developing a course. We look for an instructor knowledgeable with the technical report and involved with the development of the technical report from start to finish. This is typically a member of the task force. TRI's first choice for an instructor is usually the task force leader, followed by the co-chair or another task force member. The course developer is the project manager assigned to lead the efforts of the task force and is responsible for transferring the content of the technical report to a PowerPoint template. This template was developed by TRI staff according to theories of optimal instructional design, ensuring content is presented in a method that fosters student learning and understanding.

Once the instructor has been selected, the course developer contacts the instructor to discuss the timeline for the development process and to address any comments, concerns and/or suggestions regarding the course material. The course developer then methodically creates slides based on the content of the technical report, making sure the information presented on the slides flows accordingly, connecting ideas and concepts. The slides are formatted with words, images and diagrams to accommodate different modes of learning. In addition, any edits suggested by the instructor are incorporated into the course.

The instructor reviews the content and provides suggestions

TRI's first choice for an instructor is usually the task force leader, followed by the co-chair

and edits to improve the course. All instructors, who are subject matter experts, are asked to contribute roughly 10% of content from their experiences in the industry, in the format of supplemental slides and/or handouts that include real-life examples, exercises and case studies to personalize the presentation and add value to the course.

Once the content of the slides is finalized, the course is ready for presentation to students. Timing is critical, since the notes need to be ready when the course is scheduled, but can't be created until the technical report has been approved.

In conclusion, the development of a course that is based on a PDA technical report is a collaborative effort between many at PDA and experts in the industry. From the start, these courses have been well attended and have received very positive feedback. Popular courses include:

- "Process Validation and Verification: A Lifecycle Approach"
- "Recommended Practices for Manual Aseptic Processes"
- "Implementation of Quality Risk Management for Commercial Pharmaceutical and Biotechnology Manufacturing Operations"
- "Process Simulation Testing for Aseptically Filled Products"
- "Identification and Classification of Nonconformities in Ampoules, Syringes and Injection Devices for Pharmaceutical Manufacturers"
- "Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Validation and Ongoing Control"
- "Biofilms"

For more information about these courses and others, please visit www.pda.org/courses.

PDA Treasurer Rebecca Devine

Advancing the PDA Strategic Plan:

New Task Force Plans to Amend Technical Report No. 42 to Incorporate Lifecycle Approach

PDA's Strategic Plan is based on the three pillars of Science, People and Regulation. Continuing in our strong support of regulatory science, PDA is targeting the continued development of relevant and timely technical guidance for our membership. One area of continued interest and focus is the topic of process validation. As outlined in the January 2013 *PDA Letter*, *Technical Report 60: Process Validation: A Lifecycle Approach* was recently published and will be a guide for those developing, planning and implementing a modern process validation program.

I had the pleasure of serving on the TR-60 task force and know this new technical report will be very useful to our members. Following on the heels of *Technical Report 60,* PDA is also creating a separate task force to revise *Technical Report 42: Process Validation of Protein Manufacturing.* Published in 2005, this technical report focuses on validation of processes used in the manufacture of therapeutic proteins produced from recombinant or non-recombinant cell culture expression systems. Ultimately, the main goal of the task force behind the revision of TR-42 will be to revamp the report to more clearly reflect details of new U.S. FDA and EMA guidance documents and current practices on process validation.

An important point about TR-42 is that it has been one of the most highly used (and useful) technical reports for the PDA biotechnology membership. The goal of the new task force would be to build on the current strengths of the document, add to it and make it even better. The planned revision of TR-42 will fall under the umbrella of TR-60. Concepts outlined at a higher level in TR60 will be broken down more specifically as they apply to protein products. It is also likely that other more specific types of process validation companion documents related to various products types will be generated in the future to augment TR60.

The TR-42 task force will be charged with updating the report to specifically address the three stages of the lifecycle approach to process validation as they apply to protein manufacture. The three stages of process validation are outlined in the 2011 FDA Guidance document *Process Validation: General Principles and Practices,* and implementation is outlined in general in TR-60. While the 2005 TR-42 report does include the concept of a lifecycle approach to process validation, the three distinct stages, 1) Process Design, 2) Process Qualification, and 3) Continued Process Verification (CPV), are not addressed as specifically as in the new FDA guidance and TR-60. The revised TR-42 will delve into further detail on implementation of the concepts as they apply to the production and unit operations used for manufacture of purified proteins.

Specific details on the "how-to" or what you would do for a large molecule, specifically, say for example, in process characterization studies, in the process performance qualification, and CPV will be addressed—so TR-42 would really get into the details of the three stages for protein products. An important aspect of the revision will be strengthening the examination of how Stage 3 of the process validation approach can be implemented as the current document does not focus heavily on this aspect. In addition, ICH guidance document concepts such as risk management and knowledge management for protein product process validation will be addressed.

The new task force will likely include some members of the previous TR-60 and TR-42 task forces, as well as additional experts in protein process manufacture and validation. The task force will begin forming sometime over the next few weeks and will most likely be managed under the Biotechnology Advisory Board (BioAB).

In addition to working on companion documents to TR-60, PDA also continues to provide timely workshops in the area of process validation. A planned workshop on process validation, *Practical Implementation of the Life Cycle Approach,* will take place in Bethesda, Md. May 20-21. This will be a great chance to hear from your colleagues and regulators on global approaches to implementation of the lifecycle approach to process validation. The workshop will include information for both large and small molecules.

I am pleased that PDA continues to provide relevant, useful, and technically sound information that I use often in my work. This is certainly one of the aspects of PDA that has kept me actively involved since I joined. With direction from the Strategic Plan, I am certain this will continue to be the case.

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The Changing Validation Landscape

The perception of process validation has been changing for over a decade as regulators and industry adopt the new thinking towards continuous improvement, risk management and quality by design. These concepts, encapsulated in ICH Q9-11, are the basis for major rewrites to the process validation guidances offered by the U.S. FDA and the EMA, and inspired the recent publication of *PDA Technical Report No. 60: Process Validation — A Lifecycle Approach.*

PDA Letter Editorial Committee member **Mike Long** provides this issue's cover story, which explores important concepts in TR-60, particularly the use of risk and statistical tools to understand and control variation. Mike was a member of the TR-60 Task Force, will be discussing the topic of his article at the May PDA workshop on process validation, and intends to submit a more detailed manuscript to the PDA Journal. He also worked with fellow task force members **Scott Bozzone** and **Hal Baseman** to help the Letter's **Rebecca Stauffer** and **Katja Yount** develop this month's Infographic comparing the U.S. FDA process validation guidance with the recently revised draft EMA guidance.

Following up on Rebecca's article in the March issue on drug quality, generic injectables, and drug shortages, I interviewed **Martin VanTrieste** of Amgen for the *PDA Letter's* very first podcast! I spoke with Martin to get his thoughts on recent quality problems with injectable drugs, shortages, FDA's proposal to offer quality ratings to payors, and public perception. It was an informative and fun interview, and parts of it are excerpted in this issue. The full podcast is available at www.pda.org/pdaletter.

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New Releases at the PDA Bookstore

PDA Technical Report No. 60 (TR 60): Process Validation – A Lifecycle Approach

PDA's newest technical report, TR 60 presents timely and real world guidance for the application of a lifecycle approach to process validation. The lifecycle approach has been the focus of recent process validation guidance from major regulatory agencies and represents a significant change in expectations in this area. This new TR, part of the PCMO℠ initiative, will review requirements for process validation studies across the three-stage approach defined by the FDA and also discuss best practices for integration with supporting Quality Systems.

www.pda.org/tr60

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